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PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION for PATENT under 37 CFR 1.53(c).

Docket No.	P33070P		

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TITLE OF THE INVENTION (280 characters max)

Compounds

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ENCLOSED APPLICATION PARTS (check all that apply)

x Specification	Number of Pages	63	☐ Small Entity Statement
x Abstract	Number of Pages	1	
☐ Drawings	Number of Sheets		☐ Other (specify)

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☒ The Commissioner is hereby authorized to charge filing fees and credit Deposit Account No. **19-2570**	PROVISIONAL FILING FEE AMOUNT ($)	**$160.00**

Respectfully submitted,
Signature:

Loretta J. Henderson

Date: JUNE 26, 2002
Registration No.: 37,347

☐ Additional inventors are being named on separately numbered sheets attached hereto.

PROVISIONAL APPLICATION FILING ONLY

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PATENT TRADEMARK OFFICE

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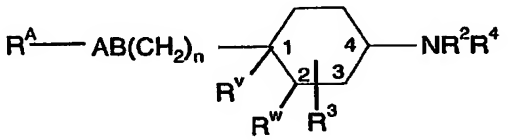
Compounds

This invention relates to novel compounds, compositions containing them and their use as antibacterials.

WO099/37635, WO00/21948, WO00/21952, WO00/43383, WO00/78748, WO01/07433, WO01/07432, WO02/08224, WO02/24684 and WO01/25227 disclose quinoline and naphthyridine derivatives having antibacterial activity.

This invention provides a compound of formula (I) or a pharmaceutically acceptable derivative thereof:

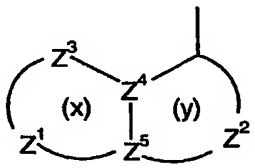


(I)

wherein:

R^V and R^W are hydrogen or R^V and R^W together are a bond;

R^A is an optionally substituted bicyclic carbocyclic or heterocyclic ring system of structure:



containing 0-3 heteroatoms in each ring in which:

at least one of rings (x) and (y) is aromatic;

one of Z^4 and Z^5 is C or N and the other is C;

Z^3 is N, NR^{13}, O, $S(O)_X$, CO, CR^1 or CR^1R^{1a};

Z^1 and Z^2 are independantly a 2 or 3 atom linker group each atom of which is independently selected from N, NR^{13}, O, $S(O)_X$, CO, CR^1 and CR^1R^{1a};

such that each ring is independently substituted with 0-3 groups R^1 and/or R^{1a};

R^1 and R^{1a} are independently selected from hydrogen; hydroxy; (C_{1-6}) alkoxy optionally substituted by (C_{1-6})alkoxy, amino, piperidyl, guanidino or amidino any of which is optionally N-substituted by one or two (C_{1-6})alkyl, acyl or (C_{1-6})alkylsulphonyl groups, CONH2, hydroxy, (C_{1-6})alkylthio, heterocyclylthio, heterocyclyloxy, arylthio, aryloxy, acylthio, acyloxy or (C_{1-6})alkylsulphonyloxy; (C_{1-6})alkoxy-substituted (C_{1-6})alkyl; hydroxy (C_{1-6})alkyl; halogen; (C_{1-6})alkyl; $(C_{1-}$

6)alkylthio; trifluromethyl; trifluoromethoxy; cyano; carboxy; nitro; azido; acyl; acyloxy; acylthio; (C_{1-6})alkylsulphonyl; (C_{1-6})alkylsulphoxide; arylsulphonyl; arylsulphoxide or an amino, piperidyl, guanidino or amidino group optionally N-substituted by one or two (C_{1-6})alkyl, acyl or (C_{1-6})alkylsulphonyl groups, or when Z^3 and the adjacent atom are CR^1 and CR^{1a}, R^1 and R^{1a} may together represent (C_{1-2})alkylenedioxy, provided that R^1 and R^{1a}, on the same carbon atom are not both optionally substituted hydroxy or amino;

provided that

(i) when R^A is optionally substituted quinolin-4-yl:

it is unsubstituted in the 6-position; or

it is substituted by at least one hydroxy (C_{1-6})alkyl, cyano or carboxy group at the 2-, 5-, 6-, 7- or 8-position; or

it is substituted by at least one trifluoromethoxy group; or

R^3 is halogen;

(ii) when R^A is optionally substituted quinazolin-4-yl, cinnolin-4-yl, 1,5-naphthyridin-4-yl, 1,7-naphthyridin-4-yl or 1,8-naphthyridin-4-yl:

it is substituted by at least one hydroxy (C_{1-6})alkyl, cyano or carboxy group at the 2-, 5-, 6-, 7- or 8-position as available; or

it is substituted by at least one trifluoromethoxy group; or

R^3 is halogen;

R^2 is hydrogen, or (C_{1-4})alkyl or (C_{2-4})alkenyl optionally substituted with 1 to 3 groups selected from:

amino optionally substituted by one or two (C_{1-4})alkyl groups; carboxy; (C_{1-4})alkoxycarbonyl; (C_{1-4})alkylcarbonyl; (C_{2-4})alkenyloxycarbonyl; (C_{2-4})alkenylcarbonyl; aminocarbonyl wherein the amino group is optionally substituted by hydroxy, (C_{1-4})alkyl, hydroxy(C_{1-4})alkyl, aminocarbonyl(C_{1-4})alkyl, (C_{2-4})alkenyl, (C_{1-4})alkylsulphonyl, trifluoromethylsulphonyl, (C_{2-4})alkenylsulphonyl, (C_{1-4})alkoxycarbonyl, (C_{1-4})alkylcarbonyl, (C_{2-4})alkenyloxycarbonyl or (C_{2-4})alkenylcarbonyl; cyano; tetrazolyl; 2-oxo-oxazolidinyl optionally substituted by R^{10}; 3-hydroxy-3-cyclobutene-1,2-dione-4-yl; 2,4-thiazolidinedione-5-yl; tetrazol-5-ylaminocarbonyl; 1,2,4-triazol-5-yl optionally substituted by R^{10}; 5-oxo-1,2,4-oxadiazol-3-yl; halogen; (C_{1-4})alkylthio; trifluoromethyl; hydroxy optionally substituted by (C_{1-4})alkyl, (C_{2-4})alkenyl, (C_{1-4})alkoxycarbonyl, (C_{1-4})alkylcarbonyl, (C_{2-4})alkenyloxycarbonyl, (C_{2-4})alkenylcarbonyl; oxo; (C_{1-4})alkylsulphonyl; (C_{2-}

4)alkenylsulphonyl; or (C_{1-4})aminosulphonyl wherein the amino group is optionally substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl;

R^3 is hydrogen; or

when R^v and R^w are a bond, R^3 is in the 2-, 3- or 4- position and when R^v and R^w are not a bond, R^3 is in the 1-, 2-, 3- or 4-position and R^3 is:
carboxy; (C_{1-6})alkoxycarbonyl; aminocarbonyl wherein the amino group is optionally substituted by hydroxy, (C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, aminocarbonyl(C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylsulphonyl, trifluoromethylsulphonyl, (C_{2-6})alkenylsulphonyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl or (C_{2-6})alkenylcarbonyl and optionally further substituted by (C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, aminocarbonyl(C_{1-6})alkyl or (C_{2-6})alkenyl; cyano; tetrazolyl; 2-oxo-oxazolidinyl optionally substituted by R^{10}; 3-hydroxy-3-cyclobutene-1,2-dione-4-yl; 2,4-thiazolidinedione-5-yl; tetrazol-5-ylaminocarbonyl; 1,2,4-triazol-5-yl optionally substituted by R^{10}; or 5-oxo-1,2,4-oxadiazol-3-yl; or

(C_{1-4})alkyl or ethenyl optionally substituted with any of the groups listed above for R^3 and/or 0 to 2 groups R^{12} independently selected from:

halogen; (C_{1-6})alkylthio; trifluoromethyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; (C_{2-6})alkenyloxycarbonyl; (C_{2-6})alkenylcarbonyl; hydroxy optionally substituted by (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylcarbonyl or (C_{2-6})alkenylcarbonyl; amino optionally mono- or disubstituted by (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylsulphonyl, (C_{2-6})alkenylsulphonyl or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl; aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, aminocarbonyl(C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl or (C_{2-6})alkenylcarbonyl and optionally further substituted by (C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, aminocarbonyl(C_{1-6})alkyl or (C_{2-6})alkenyl; oxo; (C_{1-6})alkylsulphonyl; (C_{2-6})alkenylsulphonyl; or (C_{1-6})aminosulphonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl; or

hydroxy optionally substituted by (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl or aminocarbonyl

wherein the amino group is optionally substituted by (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylcarbonyl or (C_{2-6})alkenylcarbonyl; or

amino optionally mono- or disubstituted by (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylsulphonyl, (C_{2-6})alkenylsulphonyl or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl; or

halogen;

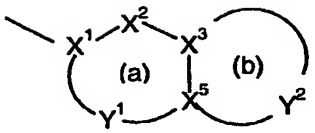
provided that when R^3 is in the 4- position it is not optionally substituted hydroxyl or amino or halogen;

in addition when R^3 is disubstituted with a hydroxy or amino containing substituent and a carboxy containing substituent these may optionally together form a cyclic ester or amide linkage, respectively;

R^{10} is selected from (C_{1-4})alkyl and (C_{2-4})alkenyl either of which may be optionally substituted by a group R^{12} as defined above; carboxy; aminocarbonyl wherein the amino group is optionally substituted by hydroxy, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylsulphonyl, trifluoromethylsulphonyl, (C_{2-6})alkenylsulphonyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl or (C_{2-6})alkenylcarbonyl and optionally further substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl; (C_{1-6})alkylsulphonyl; trifluoromethylsulphonyl; (C_{2-6})alkenylsulphonyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; (C_{2-6})alkenyloxycarbonyl; and (C_{2-6})alkenylcarbonyl;

R^4 is a group $-CH_2-R^5{}_1$ in which $R^5{}_1$ is selected from:
(C_{4-8})alkyl; hydroxy(C_{4-8})alkyl; (C_{1-4})alkoxy(C_{4-8})alkyl; (C_{1-4})alkanoyloxy(C_{4-8})alkyl; (C_{3-8})cycloalkyl(C_{4-8})alkyl; hydroxy-, (C_{1-6})alkoxy- or (C_{1-6})alkanoyloxy-(C_{3-8})cycloalkyl(C_{4-8})alkyl; cyano(C_{4-8})alkyl; (C_{4-8})alkenyl; (C_{4-8})alkynyl; tetrahydrofuryl; mono- or di-(C_{1-6})alkylamino(C_{4-8})alkyl; acylamino(C_{4-8})alkyl; (C_{1-6})alkyl- or acyl-aminocarbonyl(C_{4-8})alkyl; mono- or di-(C_{1-6})alkylamino(hydroxy) (C_{4-8})alkyl; or

R^4 is a group $-U-R^5{}_2$ where $R^5{}_2$ is an optionally substituted bicyclic carbocyclic or heterocyclic ring system (A):



(A)

containing up to four heteroatoms in each ring in which

at least one of rings (a) and (b) is aromatic;

X^1 is C or N when part of an aromatic ring or CR^{14} when part of a non aromatic ring;

X^2 is N, NR^{13}, O, $S(O)_x$, CO or CR^{14} when part of an aromatic or non-aromatic ring or may in addition be $CR^{14}R^{15}$ when part of a non aromatic ring;

X^3 and X^5 are independently N or C;

Y^1 is a 0 to 4 atom linker group each atom of which is independently selected from N, NR^{13}, O, $S(O)_x$, CO and CR^{14} when part of an aromatic or non-aromatic ring or may additionally be $CR^{14}R^{15}$ when part of a non aromatic ring,

Y^2 is a 2 to 6 atom linker group, each atom of Y^2 being independently selected from N, NR^{13}, O, $S(O)_x$, CO and CR^{14} when part of an aromatic or non-aromatic ring or may additionally be $CR^{14}R^{15}$ when part of a non aromatic ring;

each of R^{14} and R^{15} is independently selected from: H; (C_{1-4})alkylthio; halo; carboxy(C_{1-4})alkyl; halo(C_{1-4})alkoxy; halo(C_{1-4})alkyl; (C_{1-4})alkyl; (C_{2-4})alkenyl; (C_{1-4})alkoxycarbonyl; formyl; (C_{1-4})alkylcarbonyl; (C_{2-4})alkenyloxycarbonyl; (C_{2-4})alkenylcarbonyl; (C_{1-4})alkylcarbonyloxy; (C_{1-4})alkoxycarbonyl(C_{1-4})alkyl; hydroxy; hydroxy(C_{1-4})alkyl; mercapto(C_{1-4})alkyl; (C_{1-4})alkoxy; nitro; cyano; carboxy; amino or aminocarbonyl optionally substituted as for corresponding substituents in R^3; (C_{1-4})alkylsulphonyl; (C_{2-4})alkenylsulphonyl; or aminosulphonyl wherein the amino group is optionally substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl; aryl; aryl(C_{1-4})alkyl; aryl(C_{1-4})alkoxy;

each R^{13} is independently H; trifluoromethyl; (C_{1-4})alkyl optionally substituted by hydroxy, carboxy, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkoxy, (C_{1-6})alkylthio, halo or trifluoromethyl; (C_{2-4})alkenyl; aryl; aryl (C_{1-4})alkyl; arylcarbonyl; heteroarylcarbonyl; (C_{1-4})alkoxycarbonyl; (C_{1-4})alkylcarbonyl; formyl; (C_{1-6})alkylsulphonyl; or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-4})alkoxycarbonyl, (C_{1-4})alkylcarbonyl, (C_{2-4})alkenyloxycarbonyl, (C_{2-4})alkenylcarbonyl, (C_{1-4})alkyl or (C_{2-4})alkenyl and optionally further substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl;

each x is independently 0, 1 or 2;

U is CO, SO_2 or CH_2; or

R^4 is a group $-X^{1a}-X^{2a}-X^{3a}-X^{4a}$ in which:

X^{1a} is CH_2, CO or SO_2;

X^{2a} is $CR^{14a}R^{15a}$;

X^{3a} is NR^{13a}, O, S, SO_2 or $CR^{14a}R^{15a}$; wherein:

each of R^{14a} and R^{15a} is independently selected from the groups listed above for R^{14} and R^{15}, provided that R^{14a} and R^{15a} on the same carbon atom are not both selected from optionally substituted hydroxy and optionally substituted amino; or

R^{14a} and R^{15a} together represent oxo;

R^{13a} is hydrogen; trifluoromethyl; (C_{1-6})alkyl; (C_{2-6})alkenyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl, (C_{1-6})alkyl or (C_{2-6})alkenyl and optionally further substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl; or

two R^{14a} groups or an R^{13a} and an R^{14a} group on adjacent atoms together represent a bond and the remaining R^{13a}, R^{14a} and R^{15a} groups are as above defined; or

two R^{14a} groups and two R^{15a} groups on adjacent atoms together represent bonds such that X^{2a} and X^{3a} is triple bonded;

X^{4a} is phenyl or C or N linked monocyclic aromatic 5- or 6-membered heterocycle containing up to four heteroatoms selected from O, S and N and: optionally C-substituted by up to three groups selected from (C_{1-4})alkylthio; halo; carboxy(C_{1-4})alkyl; halo(C_{1-4})alkoxy; halo(C_{1-4})alkyl; (C_{1-4})alkyl; (C_{2-4})alkenyl; (C_{1-4})alkoxycarbonyl; formyl; (C_{1-4})alkylcarbonyl; (C_{2-4})alkenyloxycarbonyl; (C_{2-4})alkenylcarbonyl; (C_{1-4})alkylcarbonyloxy; (C_{1-4})alkoxycarbonyl(C_{1-4})alkyl; hydroxy; hydroxy(C_{1-4})alkyl; mercapto(C_{1-4})alkyl; (C_{1-4})alkoxy; nitro; cyano; carboxy; amino or aminocarbonyl optionally substituted as for corresponding substituents in R^3; (C_{1-4})alkylsulphonyl; (C_{2-4})alkenylsulphonyl; or aminosulphonyl wherein the amino group is optionally substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl; aryl, aryl(C_{1-4})alkyl or aryl(C_{1-4})alkoxy; and

optionally N substituted by trifluoromethyl; (C_{1-4})alkyl optionally substituted by hydroxy, (C_{1-6})alkoxy, (C_{1-6})alkylthio, halo or trifluoromethyl; (C_{2-4})alkenyl; aryl; aryl(C_{1-4})alkyl; (C_{1-4})alkoxycarbonyl; (C_{1-4})alkylcarbonyl; formyl; (C_{1-6})alkylsulphonyl; or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-4})alkoxycarbonyl, (C_{1-4})alkylcarbonyl, (C_{2-4})alkenyloxycarbonyl, (C_{2-4})alkenylcarbonyl, (C_{1-4})alkyl or (C_{2-4})alkenyl and optionally further substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl;

n is 0 or 1 and AB is $NR^{11}CO$, $CONR^{11}$, $CO\text{-}CR^8R^9$, $CR^6R^7\text{-}CO$, $O\text{-}CR^8R^9$, $CR^6R^7\text{-}O$, $NHR^{11}\text{-}CR^8R^9$, $CR^6R^7\text{-}NHR^{11}$, $NR^{11}SO_2$, $CR^6R^7\text{-}SO_2$ or $CR^6R^7\text{-}CR^8R^9$, provided that when R^V and R^W are a bond and n=0, B is not NR^{11}, O or SO_2,

or n is 0 and AB is NH-CO-NH or NH-CO-O and R^V/R^W are not a bond;
or n is 0 and AB is $CR^6R^7SO_2NR^2$, $CR^6R^7CONR^2$ or $CR^6R^7CH_2NR^2$ and R^V/R^W are not a bond;
provided that R^6 and R^7, and R^8 and R^9 are not both optionally substituted hydroxy or amino;
and wherein:
each of R^6, R^7 , R^8 and R^9 is independently selected from: H; (C_{1-6})alkoxy; (C_{1-6})alkylthio; halo; trifluoromethyl; azido; (C_{1-6})alkyl; (C_{2-6})alkenyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; (C_{2-6})alkenyloxycarbonyl; (C_{2-6})alkenylcarbonyl; hydroxy, amino or aminocarbonyl optionally substituted as for corresponding substituents in R^3; (C_{1-6})alkylsulphonyl; (C_{2-6})alkenylsulphonyl; or (C_{1-6})aminosulphonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl;
or R^6 and R^8 together represent a bond and R^7 and R^9 are as above defined;

and each R^{11} is independently H; trifluoromethyl; (C_{1-6})alkyl; (C_{2-6})alkenyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl, (C_{1-6})alkyl or (C_{2-6})alkenyl and optionally further substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl;

or where one of R^3 and R^6, R^7, R^8 or R^9 contains a carboxy group and the other contains a hydroxy or amino group they may together form a cyclic ester or amide linkage or where R^3 contains a carboxy group and A or B is NH they may be condensed to form a cyclic amide.

The invention also provides the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof in the manufacture of a medicament for use in the treatment of bacterial infections in mammals.

The invention also provides a pharmaceutical composition, in particular for use in the treatment of bacterial infections in mammals, comprising a compound of formula (I), or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable carrier.

The invention further provides a method of treatment of bacterial infections in mammals, particularly in man, which method comprises the administration to a mammal in need of such treatment of an effective amount of a a compound of formula (I), or a pharmaceutically acceptable derivative thereof.

Preferably Z^2 is three atoms long.

Preferably Z^1 is three atoms long with carbon joined to Z^3 and with R^1 on the carbon atom joined to Z^3.

In one preferred aspect, R^A is aromatic and ring (y) is fused benzene. Preferably (x) is 6-membered containing one nitrogen atom, the remainder being carbon. Most preferably Z^3 is nitrogen and the remainder are carbon.

In another preferred aspect, ring (y) is fused pyridin-4-yl (Z^2 is three atoms long, the atom attached to Z^5 in Z^2 is nitrogen and the remainder and Z^4 and Z^5 are carbon), Z^1 is two or three atoms long and Z^3 is a heteroatom such as O or S.

Suitable examples of rings R^A include optionally substituted isoquinolin-5-yl, quinolin-8-yl, thieno[3,2-b]pyridin-7-yl or 2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-8-yl

R^{13} in rings (x) and (y) is preferably H or (C_{1-6})alkyl.

When R^1 or R^{1a} is substituted alkoxy it is preferably (C_{2-6})alkoxy substitituted by optionally N-substituted amino, or (C_{1-6})alkoxy substituted by piperidyl. Suitable examples of R^1 alkoxy include methoxy, trifluoromethoxy, n-propyloxy, i-butyloxy, aminoethyloxy, aminopropyloxy, aminobutyloxy, aminopentyloxy, guanidinopropyloxy, piperidin-4-ylmethyloxy, phthalimido pentyloxy or 2-aminocarbonylprop-2-oxy.

Preferably R^1 and R^{1a} are independently hydrogen, (C_{1-4})alkoxy, (C_{1-4})alkylthio, (C_{1-4})alkyl, amino(C_{3-5})alkyloxy, nitro, cyano, carboxy, hydroxymethyl or halogen; more preferably hydrogen, methoxy, cyano, halogen or amino(C_{3-5})alkyloxy. Most preferably R^1 is methoxy or halogen and R^{1a} is H. Halogen is preferably chloro or fluoro.

R^2 is preferably hydrogen; (C_{1-4})alkyl substituted with carboxy, optionally substituted hydroxy, optionally substituted aminocarbonyl, optionally substituted amino or (C_{1-4})alkoxycarbonyl; or (C_{2-4})alkenyl substituted with (C_{1-4})alkoxycarbonyl or carboxy. More preferred groups for R^2 are hydrogen, carboxymethyl, hydroxyethyl, aminocarbonylmethyl, ethoxycarbonylmethyl, ethoxycarbonylallyl and carboxyallyl, most preferably hydrogen.

Preferred examples of R^3 include hydrogen; optionally substituted hydroxy; optionally substituted amino; halogen; (C_{1-4}) alkyl; ethenyl; optionally substituted 1-hydroxy-(C_{1-4}) alkyl; optionally substituted aminocarbonyl; carboxy(C_{1-4})alkyl; optionally substituted aminocarbonyl(C_{1-4})alkyl; cyano(C_{1-4})alkyl; optionally substituted 2-oxo-oxazolidinyl and optionally substituted 2-oxo-oxazolidinyl$(C_{1-4}$alkyl). More preferred R^3 groups are hydrogen; $CONH_2$; 1-hydroxyalkyl e.g. CH_2OH, $CH(OH)CH_2CN$; CH_2CO_2H; CH_2CONH_2; -$CONHCH_2CONH_2$; 1,2-dihydroxyalkyl e.g. $CH(OH)CH_2OH$; CH_2CN; 2-oxo-oxazolidin-5-yl; 2-oxo-oxazolidin-5-yl$(C_{1-4}$alkyl); optionally substituted hydroxy; optionally substituted amino; and halogen. Most preferably R^3 is hydrogen or hydroxy, and if hydroxy, most preferably substituted in the

1-or 3-position. R^3 hydroxy in the 3-position preferably is *trans* to NR^2R^4 and has *R* stereochemistry.

When R^3 and R^6, R^7, R^8 or R^9 together form a cyclic ester or amide linkage, it is preferred that the resulting ring is 5-7 membered. It is further preferred that the group A or B which does not form the ester or amide linkage is CH_2.

When A is CH(OH) the R-stereochemistry is preferred.

Preferably A is NH, NCH_3, CH_2, CHOH, $CH(NH_2)$, C(Me)(OH) or CH(Me).

Preferably B is CH_2 or CO.

Preferably n=0.

Preferably, when R^v and R^w are not a bond and n =1 or $AB(CH_2)_n$ is NHCONH or NHCOO, $AB(CH_2)_n$ and NR^2R^4 are cis.

Preferably, when R^v and R^w are not a bond and n=0 and AB is not NHCONH or NHCOO, $AB(CH_2)_n$ and NR^2R^4 are trans.

Most preferably:

n is 0 and either A and B are both CH_2, A is CHOH, CH_2 and B is CH_2 or A is NH and B is CO.

Preferably R^{11} is hydrogen or (C_{1-4})alkyl e.g. methyl, more preferably hydrogen.

When R^4 is $CH_2R^5{}_1$, preferably $R^5{}_1$ is (C_{6-8})alkyl.

When R^4 is a group $-X^{1a}-X^{2a}-X^{3a}-X^{4a}$:

X^{1a} is preferably CH_2.

X^{2a} is preferably CH_2 or together with X^{3a} forms a CH=CH or C≡C group.

X^{3a} is preferably CH_2, O, S or NH, or together with X^{2a} forms a CH=CH or C≡C group.

Preferred linker groups $-X^{1a}-X^{2a}-X^{3a}-$ include $-(CH_2)_2$-O-, $-(CH_2)_2$-S-, $-CH_2$-CH=CH-, $-(CH_2)_3$-, $-(CH_2)_2$-NH- or $-CH_2$CONH-.

Monocyclic aromatic heterocyclic groups for X^{4a} include pyridyl, pyrazinyl, pyrimidinyl, triazolyl, tetrazolyl, thienyl, isoimidazolyl, thiazolyl, furanyl and imidazolyl, 2H-pyridazone, 1H-pyrid-2-one. Preferred aromatic heterocyclic groups include pyrid-2-yl, pyrid-3-yl, thiazole-2-yl, pyrimidin-2-yl, pyrimidin-5-yl and fur-2-yl.

Preferred substituents on heterocyclic X^{4a} include halo especially fluoro, trifluoromethyl and nitro.

Preferred substituents on phenyl X^{4a} include halo, especially fluoro, nitro, cyano, trifluoromethyl, methyl, methoxycarbonyl and methylcarbonylamino.

Preferably X^{4a} is 2-pyridyl, 3-fluorophenyl, 3,5-difluorophenyl or thiazol-2-yl.

Preferably R^4 is $-U-R^5{}_2$.

The group –U– is preferably $-CH_2-$.

Preferably $R^5{}_2$ is an aromatic heterocyclic ring (A) having 8-11 ring atoms including 2-4 heteroatoms of which at least one is N or NR^{13} in which preferably Y^2 contains 2-3 heteroatoms, one of which is S and 1-2 are N, with one N bonded to X^3.

Alternatively and preferably the heterocyclic ring (A) has ring (a) aromatic selected from optionally substituted benzo and pyrido and ring (b) non-aromatic and Y^2 has 3-5 atoms, more preferably 4 atoms, including a heteroatom bonded to X^5 selected from O, S or NR^{13}, where R^{13} is other than hydrogen, and NHCO bonded via N to X^3, or O bonded to X^3. The ring (a) preferably contains aromatic nitrogen, and more preferably ring (a) is pyridine. Examples of rings (A) include optionally substituted:

(a) and (b) aromatic

1H-pyrrolo[2,3-b]-pyridin-2-yl, 1H-pyrrolo[3,2-b]-pyridin-2-yl, 3H-imidazo[4,5-b]-pyrid-2-yl, 3H-quinazolin-4-one-2-yl, benzimidazol-2-yl, benzo[1,2,3]-thiadiazol-5-yl, benzo[1,2,5]-oxadiazol-5-yl, benzofur-2-yl, benzothiazol-2-yl, benzo[b]thiophen-2-yl, benzoxazol-2-yl, chromen-4-one-3-yl, imidazo[1,2-a]pyridin-2-yl, imidazo-[1,2-a]-pyrimidin-2-yl, indol-2-yl, indol-6-yl, isoquinolin-3-yl, [1,8]-naphthyridine-3-yl, oxazolo[4,5-b]-pyridin-2-yl, quinolin-2-yl, quinolin-3-yl, quinoxalin-2-yl, indan-2-yl, naphthalen-2-yl, 1,3-dioxo-isoindol-2yl, benzimidazol-2-yl, benzothiophen-2-yl, 1H-benzotriazol-5-yl, 1H-indol-5-yl, 3H-benzooxazol-2-one-6-yl, 3H-benzooxazol-2-thione-6-yl, 3H-benzothiazol-2-one-5-yl, 3H-quinazolin-4-one-2-yl, 3H-quinazolin-4-one-6-yl, 4-oxo-4H-pyrido[1,2-a]pyrimidin-3-yl, benzo[1,2,3]thiadiazol-6-yl, benzo[1,2,5]thiadiazol-5-yl, benzo[1,4]oxazin-2-one-3-yl, benzothiazol-5-yl, benzothiazol-6-yl, cinnolin-3-yl, imidazo[1,2-a]pyridazin-2-yl, imidazo[1,2-b]pyridazin-2-yl, pyrazolo[1,5-a]pyrazin-2-yl, pyrazolo[1,5-a]pyridin-2-yl, pyrazolo[1,5-a]pyrimidin-6-yl, pyrazolo[5,1-c][1,2,4]triazin-3-yl, pyrido[1,2-a]pyrimdin-4-one-2-yl, pyrido[1,2-a]pyrimidin-4-one-3-yl, quinazolin-2-yl, quinoxalin-6-yl, thiazolo[3,2-a]pyrimidin-5-one-7-yl, thiazolo[5,4-b]pyridin-2-yl, thieno[3,2-b]pyridin-6-yl, thiazolo[5,4-b]pyridin-6-yl, 4-oxo-4H-pyrido[1,2-a]pyrimidin-2-yl, 1-oxo-1,2-dihydro-isoquinolin-3-yl, thiazolo[4,5-b]pyridin-5-yl, [1,2,3]thiadiazolo[5,4-b]pyridin-6-yl, 2H-isoquinolin-1-one-3-yl

(a) is non aromatic

(2S)-2,3-dihydro-1H-indol-2-yl, (2S)-2,3-dihydro-benzo[1,4]dioxine-2-yl, 3-(R,S)-3,4-dihydro-2H-benzo[1,4]thiazin-3-yl, 3-(R)-2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-3-yl, 3-(S)-2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-3-yl, 2,3-dihydro-benzo[1,4]dioxan-2-yl, 3-substituted-3H-quinazolin-4-one-2-yl,

(b) is non aromatic

1,1,3-trioxo-1,2,3,4-tetrahydro-1 l^6-benzo[1,4] thiazin-6-yl, benzo[1,3]dioxol-5-yl, 4H-benzo[1,4]oxazin-3-one-6-yl, 2,3-dihydro-benzo[1,4]dioxin-6-yl, 2-oxo-2,3-dihydro-benzooxazol-6-yl, 4H-benzo[1,4]oxazin-3-one-6-yl (3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl), 4H-benzo[1,4]thiazin-3-one-6-yl (3-oxo-3,4-dihydro-2H-benzo[1,4]thiazin-6-yl), 4H-benzo[1,4]oxazin-3-one-7-yl, 4-oxo-2,3,4,5-tetrahydro-benzo[b][1,4]thiazepine-7-yl, 5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidin-6-yl, benzo[1,3]dioxol-5-yl, 2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]thiazin-7-yl, 2-oxo-2,3-dihydro-1H-pyrido[3,4-b][1,4]thiazin-7-yl, 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazin-6-yl, 2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-6-yl, 2,3-dihydro-[1,4]dioxino[2,3-c]pyridin-7-yl, 2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-7-yl, 6,7-dihydro-[1,4]dioxino[2,3-d]pyrimidin-2-yl, 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl, 2-oxo-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yl, 2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-7-yl, 6-oxo-6,7-dihydro-5H-8-thia-1,2,5-triaza-naphthalen-3-yl, 3,4-dihydro-2H-benzo[1,4]oxazin-6-yl, 3,4-dihydro-2H-benzo[1,4]thiazin-6-yl, 3-substituted-3H-benzooxazol-2-one-6-yl, 3-substituted-3H-benzooxazole-2-thione-6-yl, 3-substituted-3H-benzothiazol-2-one-6-yl, 2,3-dihydro-1H-pyrido[2,3-b][1,4]thiazin-7-yl, 3,4-dihydro-2H-benzo[1,4]thiazin-6-yl, 3,4-dihydro-1H-quinolin-2-one-7-yl, 3,4-dihydro-1H-quinoxalin-2-one-7-yl, 6,7-dihydro-4H-pyrazolo[1,5-a]pyrimidin-5-one-2-yl, 5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl, 2-oxo-3,4-dihydro-1*H*-[1,8]naphthyridin-6-yl, 3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazin-6-yl.

R^{13} is preferably H if in ring (a) or in addition (C_{1-4})alkyl such as methyl or isopropyl when in ring (b). More preferably, in ring (b) R^{13} is H when NR^{13} is bonded to X^3 and (C_{1-4})alkyl when NR^{13} is bonded to X^5.

R^{14} and R^{15} are preferably independently selected from hydrogen, halo, hydroxy, (C_{1-4}) alkyl, (C_{1-4})alkoxy, trifluoromethoxy, nitro, cyano, aryl(C_{1-4})alkoxy and (C_{1-4})alkylsulphonyl.

More preferably R^{15} is hydrogen.

More preferably each R^{14} is selected from hydrogen, chloro, fluoro, hydroxy, methyl, methoxy, trifluoromethoxy, benzyloxy, nitro, cyano and methylsulphonyl. Most preferably R^{14} is selected from hydrogen, hydroxy, fluorine or nitro. Preferably 0-3 groups R^{14} are substituents other than hydrogen.

Most preferably R^{14} and R^{15} are each H.

Most preferred groups $R^5{}_2$ include:

[1,2,3]thiadiazolo[5,4-b]pyridin-6-yl

1H-Pyrrolo[2,3-b]pyridin-2-yl

2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-6-yl

2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-7-yl

2,3-Dihydro-[1,4]dioxino[2,3-c]pyridin-7-yl
2,3-dihydro-benzo[1,4]dioxin-6-yl
2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-7-yl
2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]thiazin-7-yl
3,4-dihydro-2H-benzo[1,4]oxazin-6-yl
3-Methyl-2-oxo-2,3-dihydro-benzooxazol-6-yl
3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl
3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl
3-oxo-3,4-dihydro-2H-benzo[1,4]thiazin-6-yl (4H-benzo[1,4] thiazin-3-one-6-yl)
4-oxo-4H-pyrido[1,2-a]pyrimidin-2-yl
6-nitro-benzo[1,3]dioxol-5-yl
7-fluoro-3-oxo-3,4-dihydro-2H-benzo[1,4] oxazin-6-yl
8-Hydroxy-1-oxo-1,2-dihydro-isoquinolin-3-yl
8-hydroxyquinolin-2-yl
benzo[1,2,3]thiadiazol-5-yl
benzo[1,2,5]thiadiazol-5-yl
benzothiazol-5-yl
thiazolo-[5,4-b]pyridin-6-yl
3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-yl
7-chloro-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-yl
7-fluoro-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-yl
2-oxo-2,3-dihydro-1*H*-pyrido[3,4-*b*][1,4]thiazin-7-yl

especially
3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl
3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-yl
7-chloro-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-yl
7-fluoro-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-yl.

When used herein, the term "alkyl" includes groups having straight and branched chains, for instance, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, pentyl and hexyl. The term 'alkenyl' should be interpreted accordingly.

Halo or halogen includes fluoro, chloro, bromo and iodo.

Haloalkyl moieties include 1-3 halogen atoms.

Unless otherwise defined, the term 'heterocyclic' as used herein includes aromatic and non-aromatic, single and fused, rings suitably containing up to four hetero-atoms in each ring selected from oxygen, nitrogen and sulphur, which rings may be unsubstituted or C-substituted by, for example, up to three groups selected from (C_{1-4})alkylthio; halo; carboxy(C_{1-4})alkyl; halo(C_{1-4})alkoxy; halo(C_{1-4})alkyl; (C_{1-4})alkyl; (C_{2-4})alkenyl;

(C_{1-4})alkoxycarbonyl; formyl; (C_{1-4})alkylcarbonyl; (C_{2-4})alkenyloxycarbonyl; (C_{2-4})alkenylcarbonyl; (C_{1-4})alkylcarbonyloxy; (C_{1-4})alkoxycarbonyl(C_{1-4})alkyl; hydroxy; hydroxy(C_{1-4})alkyl; mercapto(C_{1-4})alkyl; (C_{1-4})alkoxy; nitro; cyano; carboxy; amino or aminocarbonyl optionally substituted as for corresponding substituents in R^3; (C_{1-4})alkylsulphonyl; (C_{2-4})alkenylsulphonyl; or aminosulphonyl wherein the amino group is optionally substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl; optionally substituted aryl, aryl(C_{1-4})alkyl or aryl(C_{1-4})alkoxy and oxo groups. Each heterocyclic ring suitably has from 4 to 7, preferably 5 or 6, ring atoms. A fused heterocyclic ring system may include carbocyclic rings and need include only one heterocyclic ring. Compounds within the invention containing a heterocyclyl group may occur in two or more tautometric forms depending on the nature of the heterocyclyl group; all such tautomeric forms are included within the scope of the invention.

Where an amino group forms part of a single or fused non-aromatic heterocyclic ring as defined above suitable optional substituents in such substituted amino groups include H; trifluoromethyl; (C_{1-4})alkyl optionally substituted by hydroxy, (C_{1-6})alkoxy, (C_{1-6})alkylthio, halo or trifluoromethyl; (C_{2-4})alkenyl; aryl; aryl (C_{1-4})alkyl; (C_{1-4})alkoxycarbonyl; (C_{1-4})alkylcarbonyl; formyl; (C_{1-6})alkylsulphonyl; or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-4})alkoxycarbonyl, (C_{1-4})alkylcarbonyl, (C_{2-4})alkenyloxycarbonyl, (C_{2-4})alkenylcarbonyl, (C_{1-4})alkyl or (C_{2-4})alkenyl and optionally further substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl..

When used herein the term 'aryl', includes phenyl and naphthyl, each optionally substituted with up to five, preferably up to three, groups selected from(C_{1-4})alkylthio; halo; carboxy(C_{1-4})alkyl; halo(C_{1-4})alkoxy; halo(C_{1-4})alkyl; (C_{1-4})alkyl; (C_{2-4})alkenyl; (C_{1-4})alkoxycarbonyl; formyl; (C_{1-4})alkylcarbonyl; (C_{2-4})alkenyloxycarbonyl; (C_{2-4})alkenylcarbonyl; (C_{1-4})alkylcarbonyloxy; (C_{1-4})alkoxycarbonyl(C_{1-4})alkyl; hydroxy; hydroxy(C_{1-4})alkyl; mercapto(C_{1-4})alkyl; (C_{1-4})alkoxy; nitro; cyano, carboxy; amino or aminocarbonyl optionally substituted as for corresponding substituents in R^3; (C_{1-4})alkylsulphonyl; (C_{2-4})alkenylsulphonyl; or aminosulphonyl wherein the amino group is optionally substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl; phenyl, phenyl(C_{1-4})alkyl or phenyl(C_{1-4})alkoxy.

The term 'acyl' includes (C_{1-6})alkoxycarbonyl, formyl or (C_{1-6}) alkylcarbonyl groups.

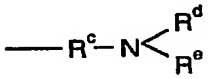
Some of the compounds of this invention may be crystallised or recrystallised from solvents such as aqueous and organic solvents. In such cases solvates may be formed. This invention includes within its scope stoichiometric solvates including hydrates as well as compounds containing variable amounts of water that may be produced by processes such as lyophilisation.

Since the compounds of formula (I) are intended for use in pharmaceutical compositions it will readily be understood that they are each provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions; these less pure preparations of the compounds should contain at least 1%, more suitably at least 5% and preferably from 10 to 59% of a compound of the formula (I) or pharmaceutically acceptable derivative thereof.

Pharmaceutically acceptable derivatives of the above-mentioned compounds of formula (I) include the free base form or their acid addition or quaternary ammonium salts, for example their salts with mineral acids e.g. hydrochloric, hydrobromic, sulphuric nitric or phosphoric acids, or organic acids, e.g. acetic, fumaric, succinic, maleic, citric, benzoic, p-toluenesulphonic, methanesulphonic, naphthalenesulphonic acid or tartaric acids. Compounds of formula (I) may also be prepared as the N-oxide. Compounds of formula (I) having a free carboxy group may also be prepared as an *in vivo* hydrolysable ester. The invention extends to all such derivatives.

Examples of suitable pharmaceutically acceptable *in vivo* hydrolysable ester-forming groups include those forming esters which break down readily in the human body to leave the parent acid or its salt. Suitable groups of this type include those of part formulae (i), (ii), (iii), (iv) and (v):


(i)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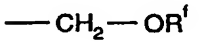
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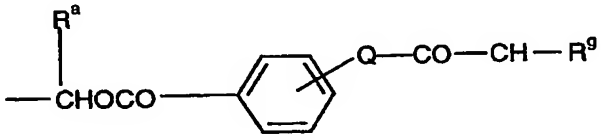
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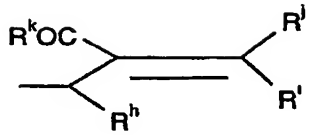
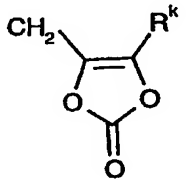


(v)

wherein R^a is hydrogen, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, methyl, or phenyl, R^b is (C_{1-6}) alkyl, (C_{1-6}) alkoxy, phenyl, benzyl, (C_{3-7}) cycloalkyl, (C_{3-7}) cycloalkyloxy, (C_{1-6}) alkyl (C_{3-7}) cycloalkyl, 1-amino (C_{1-6}) alkyl, or 1-$(C_{1-6}$ alkyl)amino (C_{1-6}) alkyl; or R^a and R^b together form a 1,2-phenylene group optionally substituted by one or two methoxy groups; R^c represents (C_{1-6}) alkylene optionally substituted with a methyl or ethyl group and R^d and R^e independently represent (C_{1-6}) alkyl; R^f represents (C_{1-6}) alkyl; R^g represents hydrogen or phenyl optionally substituted by up to three groups selected from halogen, (C_{1-6}) alkyl, or (C_{1-6}) alkoxy; Q is oxygen or NH; R^h is hydrogen or (C_{1-6}) alkyl; R^i is hydrogen, (C_{1-6}) alkyl optionally substituted by halogen, (C_{2-6}) alkenyl, (C_{1-6}) alkoxycarbonyl, aryl or heteroaryl; or R^h and R^i together form (C_{1-6}) alkylene; R^j represents hydrogen, (C_{1-6}) alkyl or (C_{1-6}) alkoxycarbonyl; and R^k represents (C_{1-8}) alkyl, (C_{1-8}) alkoxy, (C_{1-6}) alkoxy(C_{1-6})alkoxy or aryl.

Examples of suitable *in vivo* hydrolysable ester groups include, for example, acyloxy(C_{1-6})alkyl groups such as acetoxymethyl, pivaloyloxymethyl, α-acetoxyethyl, α-pivaloyloxyethyl, 1-(cyclohexylcarbonyloxy)prop-1-yl, and (1-aminoethyl)carbonyloxymethyl; (C_{1-6})alkoxycarbonyloxy(C_{1-6})alkyl groups, such as ethoxycarbonyloxymethyl, α-ethoxycarbonyloxyethyl and propoxycarbonyloxyethyl; di(C_{1-6})alkylamino(C_{1-6})alkyl especially di(C_{1-4})alkylamino(C_{1-4})alkyl groups such as dimethylaminomethyl, dimethylaminoethyl, diethylaminomethyl or diethylaminoethyl; 2-$((C_{1-6})$alkoxycarbonyl)-2-(C_{2-6})alkenyl groups such as 2-(isobutoxycarbonyl)pent-2-enyl and 2-(ethoxycarbonyl)but-2-enyl; lactone groups such as phthalidyl and dimethoxyphthalidyl.

A further suitable pharmaceutically acceptable *in vivo* hydrolysable ester-forming group is that of the formula:



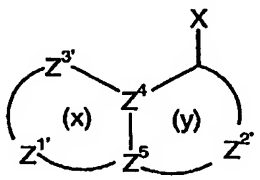
wherein R^k is hydrogen, C_{1-6} alkyl or phenyl.

R is preferably hydrogen.

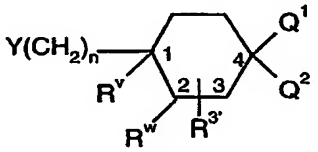
Certain of the above-mentioned compounds of formula (I) may exist in the form of optical isomers, e.g. diastereoisomers and mixtures of isomers in all ratios, e.g. racemic

mixtures. The invention includes all such forms, in particular the pure isomeric forms. For examples the invention includes compound in which an A-B group $CH(OH)-CH_2$ is in either isomeric configuration the *R*-isomer is preferred. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses..

In a further aspect of the invention there is provided a process for preparing compounds of formula (I), or a pharmaceutically acceptable derivative thereof, which process comprises reacting a compound of formula (IV) with a compound of formula (V):



(IV)



(V)

wherein n is as defined in formula (I); $Z^{1'}$, $Z^{2'}$, $Z^{3'}R^{1'}$ and $R^{3'}$ are Z^1, Z^2, Z^3, R^1 and R^3 as defined in formula (I) or groups convertible thereto; Z^4, Z^5, R^V and R^W are as defined in formula (I);

Q^1 is $NR^{2'}R^{4'}$ or a group convertible thereto wherein $R^{2'}$ and $R^{4'}$ are R^2 and R^4 as defined in formula (I) or groups convertible thereto and Q^2 is H or $R^{3'}$ or Q^1 and Q^2 together form an optionally protected oxo group;

and X and Y may be the following combinations:

(i) one of X and Y is CO_2R^y and the other is $CH_2CO_2R^x$;

(ii) X is CHR^6R^7 and Y is $C(=O)R^9$;

(iii) X is $CR^7=PR^z{}_3$ and Y is $C(=O)R^9$;

(iv) X is $C(=O)R^7$ and Y is $CR^9=PR^z{}_3$;

(v) one of Y and X is COW and the other is $NHR^{11'}$, NCO or NR11'COW;

(vi) X is $NHR^{11'}$ and Y is $C(=O)R^8$ or X is $C(=O)R^6$ and Y is $NHR^{11'}$;

(vii) X is $NHR^{11'}$ and Y is CR^8R^9W;

(viii) X is W or OH and Y is CH_2OH;

(ix) X is $NHR^{11'}$ and Y is SO_2W;

(x) one of X and Y is $(CH_2)_p$-W and the other is $(CH_2)_qNHR^{11'}$, $(CH_2)_qOH$, $(CH_2)_qSH$ or $(CH_2)_qSCOR^x$ where p+q=1;

(xi) one of X and Y is OH and the other is $-CH=N_2$;

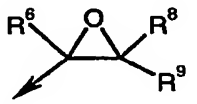
(xii) X is NCO and Y is OH or NH_2;

(xiii) X is $CR^6R^7SO_2W$, A'COW, $CR^6=CH_2$ or oxirane and Y is $NHR^{2'}$;

(xiv) Xis W and Y is $CONHR^{11}$ or $OCONH_2$

(xv) X is W and Y is -C≡CH followed by hydrogenation of the intermediate –C≡C- group;

in which W is a leaving group, e.g. halo, methanesulphonyloxy, trifluoromethanesulphonyloxy or imidazolyl; R^x and R^y are (C_{1-6})alkyl; R^z is aryl or (C_{1-6})alkyl; A' and $NR^{11'}$ are A and NR^{11} as defined in formula (I), or groups convertible thereto; and oxirane is:



wherein R^6, R^8 and R^9 are as defined in formula (I);

and thereafter optionally or as necessary converting Q^1 and Q^2 to $NR^{2'}R^{4'}$; converting A', $Z^{1'}$, $Z^{2'}$, $Z^{3'}$, $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$ and $NR^{11'}$ to A, Z^1, Z^2, Z^3, R^1, R^2, R^3, R^4 and $NR^{11'}$; converting A-B to other A-B, interconverting R^v, R^w, R^1, R^2, R^3 and/or R^4, and/or forming a pharmaceutically acceptable derivative thereof.

Process variant (i) initially produces compounds of formula (I) wherein A-B is $CO\text{-}CH_2$ or $CH_2\text{-}CO$.

Process variant (ii) initially produces compounds of formula (I) wherein A-B is $CR^6R^7\text{-}CR^9OH$.

Process variant (iii) and (iv) initially produce compounds of formula (I) wherein A-B is $CR^7{=}CR^9$.

Process variant (v) initially produces compounds of formula (I) where A-B is $CO\text{-}NR^{11}$ or $NR^{11}\text{-}CO$.

Process variant (vi) initially produces compounds of formula (I) wherein A-B is $NR^{11}\text{-}CHR^8$. or $CHR^6\text{-}NHR^{11}$.

Process variant (vii) initially produces compounds of formula (I) wherein A-B is $NR^{11'}\text{-}CR^8R^9$.

Process variant (viii) initially produces compounds of formula (I) wherein A-B is $O\text{-}CH_2$.

Process variant (ix) initially produces compounds where AB is $NR^{11}SO_2$.

Process variant (x) initially produces compounds of formula (I) wherein one of A and B is CH_2 and the other is NHR^{11}, O or S.

Process variant (xi) initially produces compounds of formul a(I) wherein A-B is OCH_2 or CH_2O.

Process variant (xii) initially produces compounds where AB is NH-CO-NH or NH-CO-O.

Process variant (xiii) initially produces compounds where n is 0 and AB is $CR^6R^7SO_2NR^2$, A'-$CONR^2$ or $CR^6R^7CH_2NR^2$.

Process variant (xiv) produces compounds where AB is $NR^{11}CO$ or NH-CO-O.

Process variant (xv) produces compounds where AB is $-CH_2CH_2-$ or –CH=CH-.

In process variants (v) and (xiii) (second variant) the reaction is a standard amide or urea formation reaction involving e.g.:

1. Activation of a carboxylic acid (e.g. to an acid chloride, mixed anhydride, active ester, O-acyl-isourea or other species), and treatment with an amine (Ogliaruso, M.A.; Wolfe, J.F. in *The Chemistry of Functional Groups (Ed. Patai, S.) Suppl. B: The Chemistry of Acid Derivatives, Pt. 1* (John Wiley and Sons, 1979), pp 442-8; Beckwith, A.L.J. in *The Chemistry of Functional Groups (Ed. Patai, S.) Suppl. B: The Chemistry of Amides (Ed. Zabricky, J.)* (John Wiley and Sons, 1970), p 73 ff. The acid and amine are preferably reacted in the presence of an activating agent such as 1-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) or 1-hydroxybenzotriazole (HOBT) or O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU); or

2. The specific methods of:

a. *in situ* conversion of an acid into the amine component by a modified Curtius reaction procedure (Shioiri, T., Murata, M., Hamada, Y., *Chem. Pharm. Bull.* 1987, 35, 2698)

b. *in situ* conversion of the acid component into the acid chloride under neutral conditions (Villeneuve, G. B.; Chan, T. H., *Tetrahedron. Lett.* 1997, 38, 6489).

A' may be, for example. protected hydroxymethylene.

The process variant (xiii) (third variant) is a standard addition reaction using methods well known to those skilled in the art. The process is preferably carried out in a polar organic solvent e.g. acetonitrile in the presence of an organic base e.g. triethylamine.

In process variant (xiii) (fourth variant) the coupling may be effected in acetonitrile at room temperature in the presence of one equivalent of lithium perchlorate as catalyst (general method of J.E. Chateauneuf *et al, J. Org. Chem.*, 56, 5939-5942, 1991) or more preferably with ytterbium triflate in dichloromethane. In some cases an elevated temperature such as 40 – 70 °C may be beneficial. Alternatively, the compound of formula (V) may be treated with a base, such as one equivalent of butyl lithium, and the resulting salt reacted with the oxirane in an inert solvent such as tetrahydrofuran, preferably at an elevated temperature such as 80°C. Use of a chiral epoxide will afford single diastereomers. Alternatively, mixtures of diastereomers may be separated by preparative HPLC or by conventional resolution through crystallisation of salts formed from chiral acids.

The process variant (xii) is a standard urea or carbamate formation reaction from the reaction of an isocyanate with an amine or alcohol and is conducted by methods well known to those skilled in the art (for example see March, J; *Advanced Organic Chemistry, Edition 3* (John Wiley and Sons, 1985), p802-3). The process is preferably carried out in a polar solvent such as N,N-dimethylformamide.

In process variant (i) the process is two step: firstly a condensation using a base, preferably sodium hydride or alkoxide, sodamide, alkyl lithium or lithium dialkylamide, preferably in an aprotic solvent e.g. ether, THF or benzene; secondly, hydrolysis using an inorganic acid, preferably HCl in aqueous organic solvent at 0-100°C. Analogous routes are described in DE330945, EP31753, EP53964 and H. Sargent, J. Am. Chem. Soc. **68**, 2688-2692 (1946). Similar Claisen methodology is described in Soszko et. al., Pr.Kom.Mat. Przyr.Poznan.Tow.Przyj.Nauk., (1962), 10, 15.

In process variant (ii) the reaction is carried out in the presence of a base, preferably organometallic or metal hydride e.g. NaH, lithium diisopropylamide or NaOEt, preferably in an aprotic solvent, preferably THF, ether or benzene at -78 to 25°C (analogous process in Gutswiller et al. (1978) J. Am. Chem. Soc. 100, 576).

In process variants (iii) and (iv) if a base is used it is preferably NaH, KH, an alkyl lithium e.g. BuLi, a metal alkoxide e.g. NaOEt, sodamide or lithium dialkylamide e.g.di-isopropylamide. An analogous method is described in US 3989691 and M.Gates et. al. (1970) J. Amer.Chem.Soc., 92, 205, as well as Taylor et al. (1972) JACS 94, 6218.

In process variant (vi) the reaction is a standard reductive alkylation using, e.g., sodium borohydride or sodium triacetoxyborohydride (Gribble, G. W. in *Encyclopedia of Reagents for Organic Synthesis (Ed. Paquette, L. A.)* (John Wiley and Sons, 1995), p 4649).

The process variant (vii) is a standard alkylation reaction well known to those skilled in the art, for example where an alcohol or amine is treated with an alkyl halide in the presence of a base (for example see March, J; *Advanced Organic Chemistry, Edition 3* (John Wiley and Sons, 1985), p364-366 and p342-343). The process is preferably carried out in a polar solvent such as N,N-dimethylformamide

In process variant (xiii) (first variant) the reaction is a standard sulphonamide formation reaction well known to those skilled in the art. This may be e.g. the reaction of a sulphonyl halide with an amine.

In process variant (viii) where X is W such as halogen, methanesulphonyloxy or trifluoromethanesulphonyloxy, the hydroxy group in Y is preferably converted to an OM group where M is an alkali metal by treatment of an alcohol with a base. The base is preferably inorganic such as NaH, lithium diisopropylamide or sodium. Where X is OH, the hydroxy group in Y is activated under Mitsunobu conditions (Fletcher et.al. J Chem

Soc. (1995), 623). Alternatively the X=O and Y=CH_2OH groups can be reacted directly by activation with 1,3-dicyclohexylcarbodiimide (DCC) (Chem. Berichte 1962, 95, 2997 or Angewante Chemie 1963 75, 377).

In process variant (ix) the reaction is conducted in the presence of an organic base such as triethylamine or pyridine such as described by Fuhrman et.al., J. Amer. Chem. Soc.; **67**, 1245, 1945. The X=$NR^{11}SO_2W$ or Y=SO_2W intermediates can be formed from the requisite amine e.g. by reaction with SO_2Cl_2 analogously to the procedure described by the same authors Fuhrman et.al., J. Amer. Chem. Soc.; **67**, 1245, 1945.

In process variant (x) where one of X and Y contains NHR^{11} the leaving group W is halogen and the reaction is a standard amine formation reaction such as direct alkylation described in (Malpass, J. R., in *Comprehensive Organic Chemistry,* Vol. 2 (Ed. Sutherland, I. O.), p 4 ff.) or aromatic nucleophilic displacement reactions (see references cited in *Comprehensive Organic Chemistry,* Vol. 6, p 946-947 (reaction index); Smith, D. M. in *Comprehensive Organic Chemistry*, Vol. 4 (Ed. Sammes, P. G.) p 20 ff.). This is analogous to the methods described in GB 1177849.

In process variant (x) where one of X and Y contains OH or SH, this is preferably converted to an OM or SM group where M is an alkali metal by treatment of an alcohol, thiol or thioacetate with a base. The base is preferably inorganic such as NaH, lithium diisopropylamide or sodium, or, for SH, metal alkoxide such as sodium methoxide. The X/Y group containing the thioacetate $SCOR^X$ is prepared by treatment of an alcohol or alkyl halide with thioacetic acid or a salt thereof under Mitsunobu conditions. The leaving group V is a halogen. The reaction may be carried out as described in Chapman et.al., J. Chem Soc., (1956),1563, Gilligan et. al., J. Med. Chem., (1992), **35**, 4344, Aloup et. al., J. Med. Chem. (1987), **30**, 24, Gilman et al., J.A.C.S. (1949), **71**, 3667 and Clinton et al., J.A.C.S. (1948), **70**, 491, Barluenga et al., J. Org. Chem. (1987) **52**, 5190. Alternatively where X is OH and Y is CH_2V, V is a hydroxy group activated under Mitsunobu conditions (Fletcher et.al. J Chem Soc. (1995), 623).

In process variant (xi) the reaction is as described in den Hertzog et. al., recl.Trav. Chim. Pays-Bas, (1950),**69**, 700.

In process variant (xiv) the leaving group W is preferably chloro, bromo or trifluoromethylsulphonyl and the reaction is the palladium catalysed process known as the "Buchwald" reaction (J. Yin and S. L. Buchwald, Org.Lett., 2000, 2, 1101).

In process variant (xv) coupling of the acetylene compound (V) with the compound (IV) is accomplished using standard Pd-mediated chemistry, for example using $Pd(Ph_3P)_2Cl_2$ as the catalyst along with the addition of CuI in a mixture of triethylamine and dimethylformamide. Hydrogenation of the intermediate –C≡C- group is carried out

conventionally over a suitable catalyst eg Pd/C, either partially to –CH=CH- or fully to –CH_2-CH_2-.

Reduction of a carbonyl group A or B to CHOH can be readily accomplished using reducing agents well known to those skilled in the art, e.g. sodium borohydride in aqueous ethanol or lithium aluminium hydride in ethereal solution. This is analogous to methods described in EP53964, US384556 and J. Gutzwiller *et al, J. Amer. Chem. Soc.*, 1978, 100, 576.

The carbonyl group A or B may be reduced to CH_2 by treatment with a reducing agent such as hydrazine in ethylene glycol, at e.g. 130-160°C, in the presence of potassium hydroxide.

Reaction of a carbonyl group A or B with an organometallic reagent yields a group where R^6 or R^8 is OH and R^7 or R^9 is alkyl.

A hydroxy group on A or B may be oxidised to a carbonyl group by oxidants well known to those skilled in the art, for example, manganese dioxide, pyridinium chlorochromate or pyridinium dichromate.

A hydroxyalkyl A-B group CHR^7CR^9OH or $CR^7(OH)CHR^9$ may be dehydrated to give the group $CR^7=CR^9$ by treatment with an acid anhydride such as acetic anhydride.

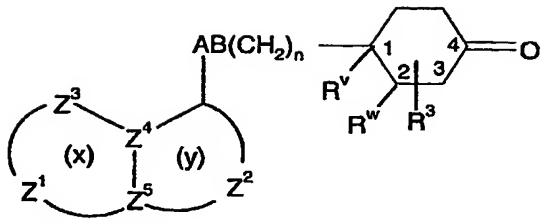
Methods for conversion of $CR^7=CR^9$ by reduction to CHR^7CHR^9 are well known to those skilled in the art, for example using hydrogenation over palladium on carbon as catalyst. Methods for conversion of $CR^7=CR^9$ to give the A-B group $CR^7(OH)CHR^9$ or CHR^7CR^9OH are well known to those skilled in the art for example by epoxidation and subsequent reduction by metal hydrides, hydration, hydroboration or oxymercuration. Where R^v and R^w together represent a bond it will be appreciated that such conversions may be inappropriate.

An amide carbonyl group may be reduced to the corresponding amine using a reducing agent such as lithium aluminium hydride.

A hydroxy group in A or B may be converted to azido by activation and displacement e.g. under Mitsunobu conditions using hydrazoic acid or by treatment with diphenylphosphorylazide and base, and the azido group in turn may be reduced to amino by hydrogenation.

An example of a group Q^1 convertible to NR^2R^4 is $NR^{2'}R^{4'}$ or halogen. Halogen may be displaced by an amine $HNR^{2'}R^{4'}$ by a conventional alkylation.

When Q^1 Q^2 together form a protected oxo group this may be an acetal such as ethylenedioxy which can subsequently be removed by acid treatment to give a compound of formula (VI):



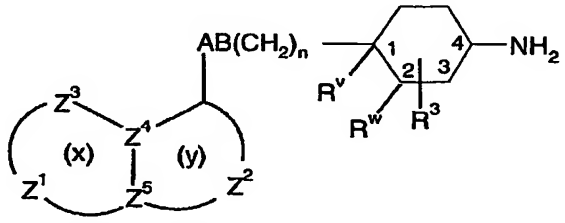
(VI)

wherein the variables are as described for formula (I)

Intermediates of formula (VI) are novel and as such form part of the invention.

The ketone of formula (VI) is reacted with an amine $HNR^{2'}R^{4'}$ by conventional reductive alkylation as described above for process variant (x).

Other novel intermediates of the invention are compounds of formula (VII):



wherein the variables are as described for formula (I).

Examples of groups $Z^{1'}$, $Z^{2'}$ and $Z^{3'}$, are $CR^{1'}$ or $CR^{1'}R^{1a'}$ where $R^{1'}$ and $R^{1a'}$ are groups convertible to R^1 and R^{1a}. $Z^{1'}$, $Z^{2'}$ and $Z^{3'}$, are preferably Z^1, Z^2 and Z^3,.

$R^{1a'}$, $R^{1'}$ and $R^{2'}$ are preferably R^{1a}, R^1 and R^2. $R^{2'}$ is preferably hydrogen. $R^{3'}$ is R^3 or more preferably hydrogen, vinyl, alkoxycarbonyl or carboxy. $R^{4'}$ is R^4 or more preferably H or an N-protecting group such as t-butoxycarbonyl, benzyloxycarbonyl or 9-fluorenylmethyloxycarbonyl.

Conversions of $R^{1a'}$, $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$ and interconversions of R^{1a}, R^1, R^2, R^3 and R^4 are conventional. In compounds which contain an optionally substituted hydroxy group, suitable conventional hydroxy protecting groups which may be removed without disrupting the remainder of the molecule include acyl and alkylsilyl groups. N protecting groups are removed by conventional methods.

For example $R^{1'}$ methoxy is convertible to $R^{1'}$ hydroxy by treatment with lithium and diphenylphosphine (general method described in Ireland et. al. (1973) J.Amer.Chem.Soc.,7829) or HBr. Alkylation of the hydroxy group with a suitable alkyl derivative bearing a leaving group such as halide and a protected amino, piperidyl, amidino or guanidino group or group convertible thereto, yields, after conversion/deprotection, R^1 alkoxy substituted by optionally N-substituted amino, piperidyl, guanidino or amidino.

R^3 alkenyl is convertible to hydroxyalkyl by hydroboration using a suitable reagent such as 9-borabicyclo[3.3.1]nonane, epoxidation and reduction or oxymercuration.

R^3 1,2-dihydroxy can be prepared from $R^{3'}$ alkenyl using osmium tetroxide or other reagents well known to those skilled in the art (see Advanced Organic Chemistry *(Ed. March, J.)* (John Wiley and Sons, 1985), p 732-737 and refs. cited therein) or epoxidation followed by hydrolysis (see Advanced Organic Chemistry *(Ed. March, J.)* (John Wiley and Sons, 1985), p 332,333 and refs. cited therein).

R^3 vinyl can be chain extended by standard homologation e.g by conversion to hydroxyethyl followed by oxidation to the aldehyde which is then subjected to a Wittig reaction.

Opening an epoxide $R^{3'}$ group with cyanide anion yields a $CH(OH)-CH_2CN$ group.

Opening an epoxide-containing $R^{3'}$ group with azide anion yields an azide derivative which can be reduced to the amine. Conversion of the amine to a carbamate is followed by ring closure with base to give the 2-oxo-oxazolidinyl containing R^3 group.

Substituents on R^3 alkyl or alkenyl may be interconverted by conventional methods, for example hydroxy may be derivatised by esterification, acylation or etherification. Hydroxy groups may be converted to halogen, thiol, alkylthio, azido, alkylcarbonyl, amino, aminocarbonyl, oxo, alkylsulphonyl, alkenylsulphonyl or aminosulphonyl by conversion to a leaving group and substitution by the required group, hydrolysis or oxidation as appropriate or reaction with an activated acid, isocyanate or alkoxyisocyanate. Primary and secondary hydroxy groups can be oxidised to an aldehyde or ketone respectively and alkyated with a suitable agent such as an organometallic reagent to give a secondary or tertiary alcohol as appropriate. A carboxylate group may be converted to an hydroxymethyl group by reduction of an ester of this acid with a suitable reducing agent such as lithium aluminium hydride.

Substituted 2-oxo-oxazolidinyl containing R^3 groups may be prepared from the corresponding aldehyde by conventional reaction with a glycine anion equivalent, followed by cyclisation of the resulting amino alcohol (M Grauert et al, Ann Chem (1985) 1817, Rozenberg et al, Angew Chem Int Ed Engl (1994) 33(1) 91). The resulting 2-oxo-oxazolidinyl group contains a carboxy group which can be converted to other R^{10} groups by standard procedures.

Carboxy groups within R^3 may be prepared by Jones' oxidation of the corresponding alcohols CH_2OH using chromic acid and sulphuric acid in water/methanol (E.R.H. Jones et al, J.C.S. 1946,39). Other oxidising agents may be used for this transformation such as sodium periodate catalysed by ruthenium trichloride (G.F.Tutwiler *et al*, J.Med.Chem., 1987, *30*(6), 1094), chromium trioxide-pyridine (G. Just *et al*, Synth. Commun. 1979, *9*(7), 613), potassium permanganate (D.E.Reedich *et al*, J. Org.

Chem.,1985,*50*(19),3535, and pyridinium chlorochromate (D. Askin *et al*, Tetrahedron Letters, 1988, 29(3), 277.

The carboxy group may alternatively be formed in a two stage process, with an initial oxidation of the alcohol to the corresponding aldehyde using for instance dimethyl sulphoxide activated with oxalyl chloride (N.Cohen *et al*, J. Am. Chem. Soc., 1983, 105, 3661) or dicyclohexylcarbodiimide (R.M.Wengler, Angew. Chim. Int. Ed. Eng., 1985, 24(2), 77), or oxidation with tetrapropylammonium perruthenate (Ley *et al*, J. Chem.Soc. Chem Commun.,1987, 1625). The aldehyde may then be separately oxidised to the corresponding acid using oxidising agents such as silver (II) oxide (R.Grigg *et al*, J. Chem. Soc. Perkin1,1983, 1929), potassium permanganate (A.Zurcher, Helv. Chim. Acta., 1987, 70 (7), 1937), sodium periodate catalysed by ruthenium trichloride (T.Sakata *et al*, Bull. Chem. Soc. Jpn., 1988, 61(6), 2025), pyridinium chlorochromate (R.S.Reddy *et al*, Synth. Commun., 1988, 18(51), 545) or chromium trioxide (R.M.Coates *et al*, J. Am. Chem. Soc.,1982, 104, 2198).

An R^3 CO_2H group may also be prepared from oxidative cleavage of the corresponding diol, $CH(OH)CH_2OH$, using sodium periodate catalysed by ruthenium trichloride with an acetonitrile-carbontetrachloride-water solvent system (V.S.Martin *et al*, Tetrahedron Letters, 1988, *29*(22), 2701).

R^3 groups containing a cyano or carboxy group may also be prepared by conversion of an alcohol to a suitable leaving group such as the corresponding tosylate by reaction with para-toluenesulphonyl chloride (M.R.Bell, J. Med. Chem.,1970, 13, 389), or the iodide using triphenylphosphine, iodine, and imidazole (G. Lange, Synth. Commun., 1990, 20, 1473). The second stage is the displacement of the leaving group with cyanide anion (LA.Paquette et al, J. Org. Chem.,1979, 44 (25), 4603; P.A.Grieco et al, J. Org. Chem.,1988, 53 (16), 3658). Finally acidic hydrolysis of the nitrile group gives the desired acids (H.Rosemeyer et al, Heterocycles, 1985, 23 (10), 2669). The hydrolysis may also be carried out with base e.g. potassium hydroxide (H.Rapoport, J. Org. Chem.,1958, 23, 248) or enzymatically (T. Beard et al, Tetrahedron Asymmetry, 1993, 4 (6), 1085).

Other functional groups in R^3 may be obtained by conventional conversions of carboxy or cyano groups.

Tetrazoles are conveniently prepared by reaction of sodium azide with the cyano group (e.g. F. Thomas et al, Bioorg. Med. Chem. Lett., 1996, *6* (6), 631; K.Kubo et al, J. Med. Chem., 1993, 36,2182) or by reaction of azidotri-n-butyl stannane with the cyano group followed by acidic hydrolysis (P.L.Ornstein, J. Org. Chem., 1994, *59*, 7682 and J. Med. Chem, 1996, *39* (11), 2219).

The 3-hydroxy-3-cyclobutene-1,2-dion-4-yl group (e.g. R.M.Soll, Bioorg. Med. Chem. Lett., 1993, *3* (4), 757 and W. A. Kinney, J. Med. Chem., 1992, 35 (25), 4720) can

be prepared by the following sequence:- (1) a compound where R3 is $(CH_2)_nCHO$ (n = 0,1,2) is treated with triethylamine, carbon tetrabromide/triphenylphosphine to give initially $(CH_2)_nCH=CBr_2$; (2) dehydrobromination of this intermediate to give the corresponding bromoethyne derivative $(CH_2)_nC\equiv CBr$ (for this 2 stage sequence see D. Grandjean et al, Tetrahedron Letters, 1994, *35* (21), 3529); (3) palladium-catalysed coupling of the bromoethyne with 4-(1-methylethoxy)-3-(tri-n-butylstannyl)cyclobut-3-ene-1,2-dione (Liebeskind et al, J. Org. Chem., 1990, *55*, 5359); (4) reduction of the ethyne moity to -CH2CH2- under standard conditions of hydrogen and palladium on charcoal catalysis(see Howard et al, Tetrahedron, 1980, *36*, 171); and finally (4) acidic hydrolysis of the methylethoxyester to generate the corresponding 3-hydroxy-3-cyclobutene-1,2-dione group (R.M.Soll, Bioorg. Med. Chem. Lett., 1993, *3* (4), 757).

The tetrazol-5-ylaminocarbonyl group may be prepared from the corresponding carboxylic acid and 2-aminotetrazole by dehydration with standard peptide coupling agents such as 1,1'-carbonyldiimidazole (P. L. Ornstein et al, J. Med Chem, 1996, *39* (11), 2232).

The alkyl- and alkenyl-sulphonylcarboxamides are similarly prepared from the corresponding carboxylic acid and the alkyl- or alkenyl-sulphonamide by dehydration with standard peptide coupling agents such as 1,1'-carbonyldiimidazole (P. L. Ornstein et al, J.Med.Chem., 1996, 39 (11), 2232).

The hydroxamic acid groups are prepared from the corresponding acids by standard amide coupling reactions eg N. R. Patel et al, Tetrahedron, 1987, *43* (22), 5375

2,4-thiazolidinedione groups may prepared from the aldehydes by condensation with 2,4-thiazolidinedione and subsequent removal of the olefinic double bond by hydrogenation.

The preparation of 5-oxo-1,2,4-oxadiazoles from nitriles is decribed by Y.Kohara et al, Bioorg. Med. Chem. Lett., 1995, *5*(17), 1903.

1,2,4-triazol-5-yl groups may be prepared from the corresponding nitrile by reaction with an alcohol under acid conditions followed by reaction with hydrazine and then an R^{10}-substituted activated carboxylic acid (see JB Polya in 'Comprehensive Heterocyclic Chemistry' Edition 1 p762, Ed AR Katritzky and CW Rees, Pergamon Press, Oxford 1984 and J.J. Ares et al, J. Heterocyclic Chem., 1991, 28(5), 1197).

The cyclohexylamine or cyclohexenylamine NH_2 is converted to NR^2R^4 by conventional means such as amide or sulphonamide formation with an acyl derivative for compounds where U or X^{1a} is CO or SO_2 or, where R^4 is $-CH_2R^5{}_1$ or U or X^{1a} is CH_2, by alkylation with an alkyl halide or other alkyl derivative R_4-W in the presence of base, acylation/reduction or reductive alkylation with an aldehyde.

Where one of R^3 and R^6, R^7, R^8 or R^9 contains a carboxy group and the other contains a hydroxy or amino group they may together form a cyclic ester or amide linkage. This linkage may form spontaneously during coupling of the compounds of formulae (IV) and (V) or in the presence of standard peptide coupling agents.

It will be appreciated that under certain circumstances interconvertions may interfere, for example, hydroxy groups in A or B and the cyclohexyl- or cyclohexenylamine will require protection e.g. as a carboxy- or silyl-ester group for hydroxy and as an acyl derivative for nitrogen, during conversion of $R^{1a'}$, $R^{1'}$, $R^{2'}$, $R^{3'}$ or $R^{4'}$, or during the coupling of the compounds of formulae (IV) and (V).

Compounds of formulae (IV) and (V) are known compounds, (see for example Smith *et al, J. Amer. Chem. Soc.*, 1946, 68, 1301) or prepared analogously, see for example the references cited above.

Compounds of formula (IV) where X is $CR^6R^7SO_2W$ may be prepared by a route analogous to that of Ahmed El Hadri *et al, J. Heterocyclic Chem.*, 1993, 30(3), 631. Thus compounds of formula (IV) where X is CH_2SO_2OH may be prepared by reacting the corresponding 4-methyl compound with N-bromosuccinimide, followed by treatment with sodium sulfite. The leaving group W may be converted to another leaving group W, e.g. a halogen group, by conventional methods.

The isocyanate of formula (IV) may be prepared conventionally from a 4-amino derivative such as 4-amino-quinoline, and phosgene, or phosgene equivalent (eg triphosgene) or it may be prepared more conveniently from a 4-carboxylic acid by a "one-pot" Curtius Reaction with diphenyl phosphoryl azide (DPPA) [see T. Shiori et al. *Chem. Pharm. Bull.* 35, 2698-2704 (1987)].

The 4-amino derivatives are commercially available or may be prepared by conventional procedures from a corresponding 4-chloro derivative by treatment with ammonia (O.G. Backeberg et. al., J. Chem Soc., 381, 1942) or propylamine hydrochloride (R. Radinov et. al., Synthesis, 886, 1986).

4-Alkenyl compounds of formula (IV) may be prepared by conventional procedures from a corresponding 4-halogeno-derivative by e.g. a Heck synthesis as described in e.g. *Organic Reactions*, 1982, 27, 345.

4-Halogeno derivatives of compounds of formula (IV) are commercially available, or may be prepared by methods known to those skilled in the art. A 4-chloroquinoline is prepared from the corresponding quinolin-4-one by reaction with phosphorus oxychloride ($POCl_3$) or phosphorus pentachloride, PCl_5 A-4-bromo-substituent may be prepared from the quinolin- or naphthyridin-4-one by reaction with phosphorus tribromide (PBr3) in DMF. A 4-chloroquinazoline is prepared from the corresponding quinazolin-4-one by reaction with phosphorus oxychloride ($POCl_3$) or phosphorus pentachloride, PCl_5. A

quinazolinone and quinazolines may be prepared by standard routes as described by T.A. Williamson in *Heterocyclic Compounds*, 6, 324 (1957) Ed. R.C. Elderfield.

Activated carboxy derivatives X=A'COW of formula (IV) may be prepared from X=A'CO_2H derivatives in turn prepared from CO_2H derivatives by conventional methods such as homologation.

4-Carboxy derivatives of compounds of formula (IV) are commercially available or may be prepared by conventional procedures for preparation of carboxy heteroaromatics well known to those skilled in the art. For example, quinazolines may be prepared by standard routes as described by T.A. Williamson in *Heterocyclic Compounds*, 6, 324 (1957) Ed. R.C. Elderfield. These 4-carboxy derivatives may be activated by conventional means, e.g. by conversion to an acyl halide or anhydride.

4-Carboxy derivatives such as esters may be reduced to hydroxymethyl derivatives with for example lithium aluminium hydride. Reaction with mesyl chloride and triethylamine would give the mesylate derivative. A diazo compound (X is $-CH=N_2$) may be prepared from the 4-carboxaldehyde via the tosyl hydrazone. The 4-carboxaldehyde may be obtained from from the acid by standard procedures well known to those skilled in the art.

A 4-oxirane derivative of compounds of formula (IV) is conveniently prepared from the 4-carboxylic acid by first conversion to the acid chloride with oxalyl chloride and then reaction with trimethylsilyldiazomethane to give the diazoketone derivative. Subsequent reaction with 5M hydrochloric acid gives the chloromethylketone. Reduction with sodium borohydride in aqueous methanol gives the chlorohydrin which undergoes ring closure to afford the epoxide on treatment with base, e.g. potassium hydroxide in ethanol-tetrahydrofuran.

Alternatively and preferably, 4-oxirane derivatives can be prepared from bromomethyl ketones which can be obtained from 4-hydroxy compounds by other routes well known to those skilled in the art. For example, hydroxy compounds can be converted to the corresponding 4-trifluoromethanesulphonates by reaction with trifluoromethanesulphonic anhydride under standard conditions (see K. Ritter, Synthesis, 1993, 735). Conversion into the corresponding butyloxyvinyl ethers can be achieved by a Heck reaction with butyl vinyl ether under palladium catalysis according to the procedure of W. Cabri *et al*, J. Org. Chem, 1992, **57** (5), 1481. (Alternatively, the equivalent intermediates can be attained by Stille coupling of the trifluoromethanesulphonates or the analaogous chloro derivatives with (1-ethoxyvinyl)tributyl tin, (T. R. Kelly, J. Org. Chem., 1996, **61**, 4623).) The alkyloxyvinyl ethers are then converted into the corresponding bromomethylketones by treatment with N-bromosuccinimide in aqueous

tetrahydrofuran in a similar manner to the procedures of J. F. W. Keana, J. Org. Chem., 1983, **48**, 3621 and T. R. Kelly, J. Org. Chem., 1996, **61**, 4623.

The 4-hydroxyderivatives can be prepared from an aminoaromatic by reaction with methylpropiolate and subsequent cyclisation, analogous to the method described in N. E. Heindel et al, J. Het. Chem., 1969, **6**, 77. For example, 5-amino-2-methoxy pyridine can be converted to 4-hydroxy-6-methoxy-[1,5]naphthyridine using this method.

If a chiral reducing agent such as (+) or (-)-B-chlorodiisopinocamphenylborane ['DIP-chloride'] is substituted for sodium borohydride, the prochiral chloromethylketone is converted into the chiral chlorohydrin with ee values generally 85-95% [see C. Bolm *et al, Chem. Ber.* 125, 1169-1190, (1992)]. Recrystallisation of the chiral epoxide gives material in the mother liquor with enhanced optical purity (typically ee 95%).

The (*R*)-epoxide, when reacted with an amine derivative gives ethanolamine compounds as single diastereomers with (*R*)-stereochemistry at the benzylic position.

Alternatively, the epoxide may be prepared from the 4-carboxaldehyde by a Wittig approach using trimethylsulfonium iodide [see G.A. Epling and K-Y Lin, *J. Het. Chem.*, 1987, 24, 853-857], or by epoxidation of a 4-vinyl derivative.

Pyridazines may be prepared by routes analogous to those described in Comprehensive Heterocyclic Chemistry, Volume 3, Ed A.J. Boulton and A. McKillop and napthyridines may be prepared by routes analogous to those described in Comprehensive Heterocyclic Chemistry, Volume 2, Ed A.J. Boulton and A. McKillop.

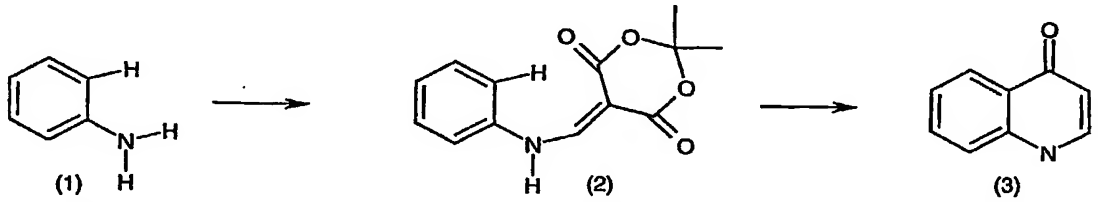
4-Hydroxy-1,5-naphthyridines can be prepared from 3-aminopyridine derivatives by reaction with diethyl ethoxymethylene malonate to produce the 4-hydroxy-3-carboxylic acid ester derivative with subsequent hydrolysis to the acid, followed by thermal decarboxylation in quinoline (as for example described for 4-Hydroxy-[1,5]naphthyridine-3-carboxylic acid, J. T. Adams *et al., J.Amer.Chem.Soc.*, 1946, **68**, 1317). A 4-hydroxy-[1,5]naphthyridine can be converted to the 4-chloro derivative by heating in phosphorus oxychloride, or to the 4-methanesulphonyloxy or 4-trifluoromethanesulphonyloxy derivative by reaction with methanesulphonyl chloride or trifluoromethanesulphonic anhydride, respectively, in the presence of an organic base. A 4-amino 1,5-naphthyridine can be obtained from the 4-chloro, 4-methanesulphonyloxy or 4-trifluoromethanesulphonyloxy derivative by reaction with n-propylamine in pyridine.

Similarly, 6-methoxy-1,5-naphthyridine derivatives can be prepared from 3-amino-6-methoxypyridine.

1,5-Naphthyridines may be prepared by other methods well known to those skilled in the art (for examples see P.A. Lowe in "Comprehensive Heterocyclic Chemistry" Volume 2, p581-627, Ed A.R. Katritzky and C.W. Rees, Pergamon Press, Oxford, 1984).

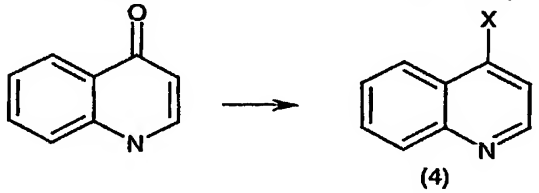
The 4-hydroxy and 4-amino-cinnolines may be prepared following methods well known to those skilled in the art [see A.R. Osborn and K. Schofield, *J. Chem. Soc.* 2100 (1955)]. For example, a 2-aminoacetophenone is diazotised with sodium nitrite and acid to produce the 4-hydroxycinnoline with conversion to chloro and amino derivatives as described for 1,5-naphthyridines.

R^A groups where the ring (y) is 4-pyridyl are available by the sequence described below, starting from an aromatic or heterocyclic amine (1), with at least one free CH position adjacent to the amine. Reaction with Meldrum's acid and trimethyl orthformate in ethanol at reflux affords the corresponding 2,2-dimethyl-5-phenylaminomethylene-[1,3]dioxane-4,6-dione derivatives (2). These can be cyclised at elavated temperatures (180-220°C) in inert solvents such as Dowtherm to give the corresponding 1H-quinolin-4-one or heterocyclic derivatives (3). These processes are well-established and are described by Walz and Sundberg (J. Org. Chem., 2000, **65** (23), 8001) and by Todter and Lackner (Synthesis, 1997 (5) 576).



(1) (2) (3)

Activation of the quinolone species related to (3) into the corresponding 4-quinolyl bromides (4) can be accomplished with phosphorous oxybromide or more preferably phosphorous tribromide in N,N-dimethylformamide (see M. Schmittel *et al*, Synlett, 1997, (9), 1096 and K. Gould *et al*, J. Med., Chem., 1988, **31** (7), 1445). The corresponding chlorides (5) are available by using phosphoryl oxychloride (for instance C. W. Wright *et al*, J. Med., Chem., 2001, **44** (19), 3187).

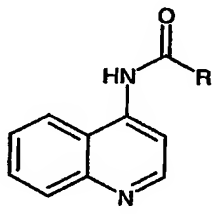


(4)

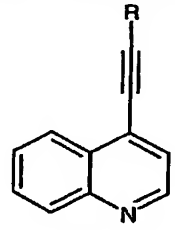
(4) X = Br
(5) X = Cl
(6) X = OTf

Alternatively, the quinolone species may be activated to the corresponding 1,1,1-trifluoro-methanesulfonic acid quinolin-4-yl esters (6) by the action of agents such as triflic anhydride or more preferably N-trifluoromethanesulphonimide (see for example M. Alvarez *et al*, Tet 2000, **56** (23) 3703; M. Alvarez *et al*, Eur. J. Org., Chem., 2000, (5), 849; J. Joule *et al*, Tet, 1998, **54** (17), 4405; J. K. Stille *et al*, J.A.C.S., 1988, **110** (12), 4051).

Activated species such as (4), (5), and (6) can then be subjected to a variety of metal-catalysed coupling reactions, such as amidation with primary carboxamides to give compounds such as (7) following the procedures of S. L. Buchwald et al (J.A.C.S., 2001, **123**, 4051 and 7727; Org. Lett., 1999, **1**, 35) or Sonogashira coupling with acetylenes to give compounds such as (8) (see A. Droz *et al*, Helv. Chim. Acta., 2001, **84** (8), 2243; M. Belly *et al*, Synlett, 2001 (2), 222; M. Pirrung *et al*, J.A.C.S., 2001, **123** (16), 3638).



(7)



(8)

R^A thieno[3,2-b]pyridin-7-yl, 2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-8-yl, quinolin-8-yl and isoquinolin-5-yl derivatives are commercially available or prepared by conventional methods from commercially available or literature derivatives, for example 4H-thieno[3,2-b]pyridin-4-one, 2,3-dihydro-[1,4]dioxino[2,3-b]pyridine (prepared by the method of H. Neunhoffer *et al*, Chem., Ber., 1990, **123**), 2-methoxy-quinolin-8-ylamine (prepared by the method of K. Mislow et al J.A.C.S. **68**, 1353 (1946)), 2,8-quinolinediol or trifluoromethane sulphonic acid-isoquinolin-5-yl ester (prepared as in D. Ortwine et al, J. Med. Chem., 1992, **35** (8), 1345).

The compounds of formula (V) are either commercially available or may be prepared by conventional methods.

For compounds of formula (V), where Y is NHR^{11} suitable amines may be prepared from the corresponding 4-substituted cyclohexyl- or cyclohexenyl acid or alcohol. In a first instance, an N-protected cyclohexyl- or cyclohexenyl amine containing an acid bearing substituent, can undergo a Curtius rearrangement and the intermediate isocyanate can be converted to a carbamate by reaction with an alcohol. Conversion to the amine may be achieved by standard methods well known to those skilled in the art used for amine protecting group removal. For example, an acid substituted N-protected cyclohexyl- or cyclohexenyl amine can undergo a Curtius rearrangement e.g. on treatment with diphenylphosphoryl azide and heating, and the intermediate isocyanate reacts in the presence of 2-trimethylsilylethanol to give the trimethylsilylethylcarbamate (T.L. Capson & C.D. Poulter, *Tetrahedron Lett.*, 1984, 25, 3515). This undergoes cleavage on treatment with tetrabutylammonium fluoride to give the 4-amine substituted N-protected compound of formula (V). Alternatively, an acid group $(CH_2)_{n-1}CO_2H$ may be converted to $(CH_2)_nNHR^{11}$ by reaction with an activating agent such as isobutyl

chloroformate followed by an amine $R^{11}NH_2$ and the resulting amide reduced with a reducing agent such as $LiAlH_4$.

In a second instance, an N-protected cyclohexyl- or cyclohexenyl amine containing an alcohol bearing substituent undergoes a Mitsunobu reaction (for example as reviewed in Mitsunobu, *Synthesis*, (1981), 1), for example with succinimide in the presence of diethyl azodicarboxylate and triphenylphosphine to give the phthalimidoethylcyclohexyl- or cyclohexenyl amine. Removal of the phthaloyl group, for example by treatment with methylhydrazine, gives the amine of formula (V).

Compounds of formula (V) where n=1 may be prepared from the compound where n=0 by homologation eg starting from a compound of formula (V) where $Y=CO_2H$.

Compounds of formula (V) with a $-C\equiv CH$ group may be prepared from the ketone treated with trimethylsilylacetylene and n-butyl lithium in dimethylformamide at low temperature followed by removal of the trimethylsilyl group with potassium carbonate in methanol or a fluoride source such as KF or tetrabutylammonium fluoride.

Compounds of formula (V) with a $-CONHR^{11}$ group may be prepared from the corresponding nitrile by partial hydrolysis with with concentrated mineral acid at ambient temperature, such as concentrated hydrochloric acid (M. Brown *et al*, J. Med. Chem., 1999, **42**, (9), 1537) or with concentrated sulphuric acid (F. Macias *et al* Tetrahedron, 2000, **56**, (21), 3409).

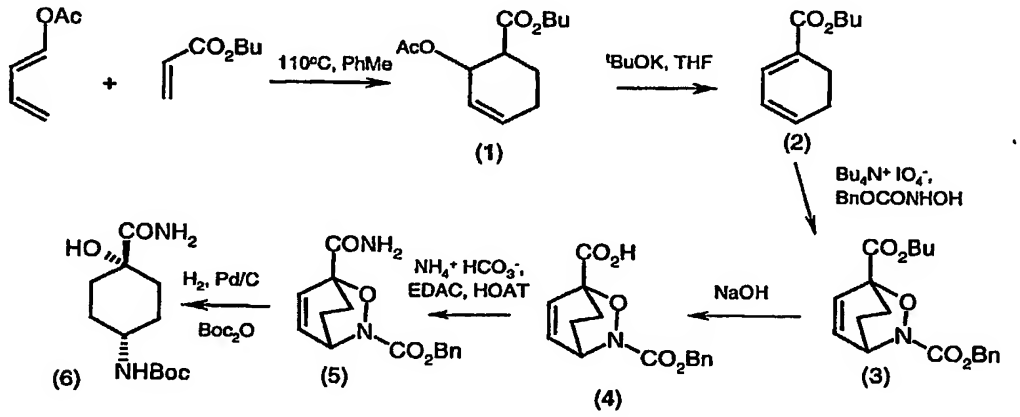
Compounds of formula (V) with a $-OCONH_2$ group may be prepared from the corresponding alcohol by reaction with phosgene followed by ammonia.

Compounds of formula (V) substituted by R^3 at the 1- or 4-position may be prepared from a 1-keto derivative via a cyanohydrin reaction with sodium cyanide/hydrochloric acid in an ether/water two phase system (J. Marco *et al* Tetrahedron, 1999, **55**, (24), 7625), or using trimethylsilylcyanide and zinc iodide catalysis in dichloromethane (A. Abad et al, J. Chem. Soc., Perkin 1, 1996, **17**, 2193), followed by hydrolysis by heating in concentrated hydrochloric acid to give the α-hydroxy acid (Compound(V), $Y=CO_2H$, n=0, $R^{3'}$ =OH and Q^1 is $NR^{2'}R^{4'}$) or partial hydrolysis to the carboxamide $-CONH_2$ as described above. In examples where there is trimethylsilyl protection of the alcohol, this is removed under the acidic conditions of cyanide hydrolysis. It will be appreciated that the amine protecting group eg N-carboxylic acid *tert*-butyl ester is concommitantly removed during the acid hydrolysis step, necessitating a standard reprotection with di-*tert*-butyl dicarbonate, giving key intermediates (V) such as (4-carbamoyl-4-hydroxy-cyclohexyl)-carbamic acid *tert*-butyl ester. It is noteworthy that during the cyanohydrin formation there is little or no stereoselectivity with regard to relative stereochemistry, and the (4-carbamoyl-4-hydroxy-cyclohexyl)-carbamic acid *tert*-

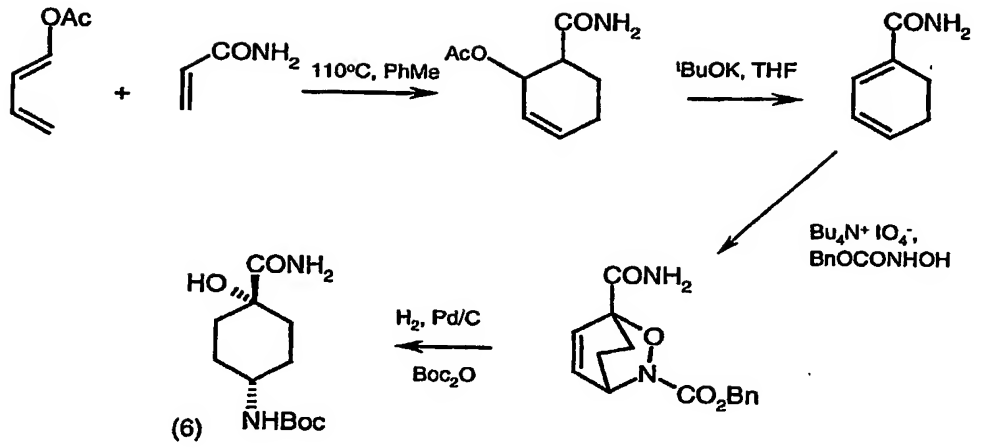
butyl ester produced in this process is a mixture of *cis* and *trans* stereoisomers. These isomers can be separated by careful chromatography.

The same 1-keto-derivative could undergo a Wittig reaction with $Ph_3PCH=CO_2Me$ to give the α,β-unsaturated carboxylic ester MeO_2C-CH=C<Ring, which could be epoxidised (eg meta-chloroperbenzoic acid) to give the α,β-epoxy-ester. Alternatively this could be formed directly from the keto-derivative via a glycidic ester condensation with an α-halogeno-ester. Base hydrolysis would afford the α,β-epoxy-carboxylic acid, which on reduction (eg lithium triethylborohydride – see J. Miklefield et al J. Amer. Chem. Soc. 117, 1153-1154 (1995) or hydrogenation over platinum oxide (see Artamonow Zh.Obshch.Khim. 28 1355-1359 (1958)) would afford the β-hydroxy acid (Compound (V) $Y=CO_2H$, n=1, $R^{3'}$ =OH). Alternatively a Reformatsky reaction with the keto-derivative and an α-bromocarboxylic acid ester and zinc, followed by acid hydrolysis would afford the β-hydroxycarboxylic acid directly. The 1-keto-derivative could also undergo a Strecker type synthesis via a Bucherer-Bergs procedure (potassium cyanide/ammonium carbonate) [see T. Scott Yokum et al. Tetrahedron Letters, 38, 4013-4016 (1997)] to give the α-amino-carboxylic acid (Compound (V) $Y=CO_2H$, n=0, $R^{3'}$ =NH_2).

An alternative route to 1-substituted compounds (V) involves a Diels Alder reaction between butyl acrylate and acetoxy butadiene to give (1). Elimination of acetic acid and hetero Diels Alder reaction with an *in-situ* generated acyl nitroso compound gives the bicyclic hydroxylamine product (3). The ester is transformed to an amide in two steps, and catalytic hydrogenation is used to reduce the double bond, remove the nitrogen protection and cleave the NO bond. After reprotection of the amino group, the cyclohexane amide with the required stereochemistry is obtained.

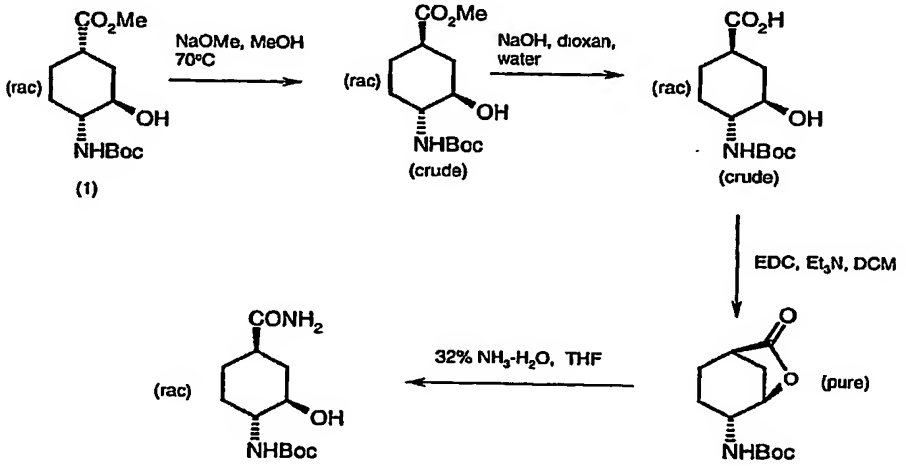


Two steps can be avoided by starting with acrylamide :

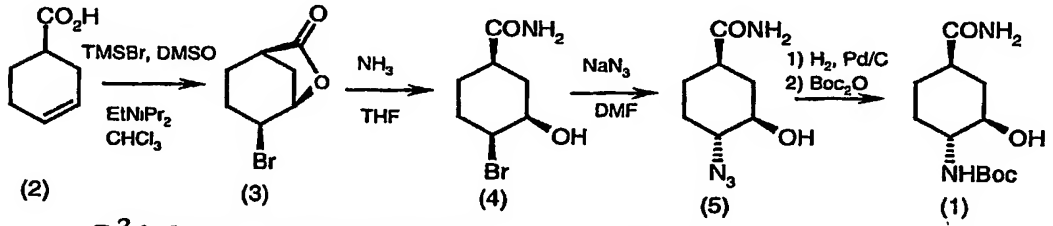


Compounds of formula (V) substituted by R^3 at the 2- or 3-position may be prepared from the corresponding substituted phenyl derivative 1-Y$(CH_2)_n$Ph(-R3)-4-NR_2 (eg where Y=carboxylic acid) by hydrogenation at elevated temperature and pressure using a Pt or Ru catalyst.

Compounds of formula (V) with a 3-hydroxyl group may be prepared from a 3,4 oxirane-cyclohexane carboxylic acid by reaction with an amine NHR^2R^4 or azide (followed by conversion of the azide to amino). [See for example K. Krajewski et al. Tetrahedron Asymmetry 10, 4591-4598 (1999)]. The ester group may be epimerised by heating in strong base, hydrolysed to the carboxylic acid and cyclised to the lactone using a conventional coupling reagent (EDC) . Other conventional reagents eg DCC, Im_2CO, HATU etc. may also be used. The lactone is readily purified by chromatography. The lactone is readily opened with aqueous ammonia in tetrahydrofuran to give the required (racemic) amide.



An improved procedure starting from 3-cyclohexene carboxylic acid may be used to prepare single enantiomers. 3-Cyclohexene carboxylic acid (2) is resolved via α-Me benzylamine salt (Schwartz et al, J. Am. Chem. Soc., **100**, 5199, (1978)). A higher yield of lactone (3) can be achieved using a larger excess of reagents. Lactone opening with ammonia gives (4), which is treated with azide to give (5) which has the required *trans* relative stereochemistry between the amide and N-substituent. Finally, azide reduction and Boc protection gives (1) a compound of formula (V).



R^3 halogen can be introduced onto a cyclohexane ring via treatment of a silyl enol ether with an electrophilic halogenating, such as a fluorinating, agent. For example,ethyl-4-oxo cyclohexanecarboxylate is converted to its TMS enol ether (S-W Lin, Bioorg.Med.Chem.Lett, 10; 11; 1297 – 1298, 2000). This conversion may be carried out using an optically active base to give enantiomerically enriched material [KW Henderson et al, JCS Chem Comm, 479-480, (2000); NS Simpkins et al, Tet. Lett, **30**, 51, 7241-7244, (1989); K Koga et al, J. Am. Chem. Soc., **108**, 543-545, (1986); P Knochel, Ang. Chem. Int. Ed., **37**, (21), 3014-3016 (1998); VK Aggarwal, J. Chem. Soc. Perkin Trans. 1, 2883 (1999)]. Treatment with an electrophilic fluorinating agent, for example Selectfluor, yields the α-fluoroketones which may be separated by silica gel chromatography. Reductive amination with an amine, for example benzylamine or a chiral benzylamine for example α -methyl benzylamine using sodium cyanoborohydride or sodium triacetoxyborohydride yields the amino ester. Diastereoisomers may be separated by an appropriate combination of silica gel chromatography, HPLC and crystallisation of the free base or a suitable salt.

R^4-halides and R^4-W derivatives, acyl derivatives or aldehydes are commercially available or are prepared conventionally. The aldehydes may be prepared by partial reduction of the corresponding ester with lithium aluminium hydride or di-isobutylaluminium hydride or more preferably by reduction to the alcohol, with lithium aluminium hydride or sodium borohydride (see *Reductions by the Alumino- and Borohydrides in Organic Synthesis*, 2nd ed., Wiley, N.Y., 1997; *JOC*, 3197, 1984; *Org. Synth. Coll.*, 102, 1990; 136, 1998; *JOC*, 4260, 1990; *TL*, 995, 1988; *JOC*, 1721, 1999; *Liebigs Ann./Recl.*, 2385, 1997; *JOC*, 5486, 1987) , followed by oxidation to the aldehyde with manganese (II) dioxide, or by a 'Swern' procedure (oxalyl chloride/DMSO), or by using potassium dichromate (PDC). The aldehydes may also be prepared from carboxylic

acids in two stages by conversion to a mixed anhydride for example by reaction with isobutyl chloroformate followed by reduction with sodium borohydride (R. J. Alabaster et al., Synthesis, 598, 1989) to give the hydroxymethyl substituted heteroaromatic or aromatic and then oxidation with a standard oxidising agent such as pyridinium dichromate or manganese (II) dioxide. Acyl derivatives may be prepared by activation of the corresponding ester. R^4-halides such as bromides may be prepared from the alcohol R^4OH by reaction with phosphorus tribromide in dichloromethane/triethylamine. Where X^{2a} is CO and X^{3a} is NR^{13a} the R^4-halide may be prepared by coupling an X^{4a}-NH_2 amine and bromoacetyl bromide. R^4-W derivatives such as methanesulphonyl derivatives may be prepared from the alcohol R^4OH by reaction with methane sulphonyl chloride. The leaving group W may be converted to another leaving group W, e.g. a halogen group, by conventional methods. Alternatively the aldehyde $R^5{}_2CHO$ and sulphonic acid derivative $R^5{}_2SO_2W$ may be generated by treatment of the $R^5{}_2H$ heterocycle with suitable reagents. For example benzoxazinones, or more preferably their N-methylated derivatives can be formylated with hexamine in either trifluoroacetic acid or methanesulfonic acid, in a modified Duff procedure [O. I. Petrov et al. *Collect. Czech. Chem. Commun.* **62**, 494-497 (1997)]. 4-Methyl-4H-benzo[1,4]oxazin-3-one may also be formylated using dichloromethyl methyl ether and aluminium chloride giving exclusively the 6-formyl derivative.

Reaction of a $R^5{}_2H$ heterocycle with chlorosulphonic acid gives the sulphonic acid derivative (by methods analogous to Techer *et. al., C.R.Hebd. Seances Acad. Sci. Ser.C*; **270**, 1601, 1970).

The aldehyde $R^5{}_2CHO$ may be generated by conversion of an $R^5{}_2$halogen or $R^5{}_2$trifluoromethane sulphonyloxy derivative into an olefin with subsequent oxidative cleavage by standard methods. For example, reaction of a bromo derivative under palladium catalysis with trans-2-phenylboronic acid under palladium catalysis affords a styrene derivative which upon ozonolysis affords the required $R^5{}_2CHO$ (Stephenson, G. R., Adv. Asymmetric Synth. (1996), 275-298. Publisher: Chapman & Hall, London).

Where $R^5{}_2$ is an optionally substituted benzoimidazol-2-yl group, the compound of formula (V) where $R^{4'}$ is R^4 may be obtained by converting a $R^{4'}$ cyanomethyl group with partial hydrolysis to give the 2-ethoxycarbonimidoylethyl group which can then be condensed with an appropriately substituted 1,2-diaminobenzene to give the required benzoimidazol-2-yl group.

$R^5{}_2H$ heterocycles are commercially available or may be prepared by conventional methods. For example where a benzoxazinone is required, a nitrophenol may be alkylated with for example ethyl bromoacetate and the resulting nitro ester reduced with Fe in acetic acid (alternatively Zn/AcOH/HCl or H_2/Pd/C or H_2/Raney Ni).

The resulting amine may undergo spontaneous cyclisation to the required benzoxazinone, or cyclisation may be induced by heating in acetic acid. Alternatively a nitrophenol may be reduced to the aminophenol, which is reacted with chloroacetyl chloride [method of X. Huang and C. Chan, *Synthesis* 851 (1994)] or ethyl bromoacetate in DMSO [method of Z. Moussavi et al. *Eur. J. Med. Chim. Ther.* **24**, 55-60 (1989)]. The same general routes can be applied to prepare benzothiazinones [See for example F. Eiden and F. Meinel, Arch. Pharm. 312, 302-312 (1979), H. Fenner and R Grauert *Liebigs. Ann. Chem.* 193-313 (1978)]]. A variety of routes are available to prepare aza analogues of benzothiazinones via the key corresponding aldehydes. For instance, 2-oxo-2,3-dihydro-1*H*-pyrido[3,4-b][1,4]thiazine-7-carbaldehyde may be accessed from 5-fluoro-2-picoline (E. J. Blanz, F. A. French, J. R. DoAmaral and D. A. French, J. Med. Chem. **1970**, *13*, 1124-1130) by constructing the thiazinone ring onto the pyridyl ring then functionalising the methyl substituent. The dioxin analogue of this aza substitution patern, 2,3-dihydro-[1,4]dioxino[2,3-c]pyridine-7-carbaldehyde is accessible from Kojic acid by aminolysis from pyrone to pyridone then annelating the dioxin ring. Other aza substitution patterns with pyridothiazin-3-one, pyridooxazin-3-one, and pyridodioxin ring systems are also accessible. Ortho-aminothiophenols may be conveniently prepared and reacted as their zinc complexes [see for example V. Taneja et al *Chem. Ind.* 187 (1984)]. Benzoxazolones may be prepared from the corresponding aminophenol by reaction with carbonyl diimidazole, phosgene or triphosgene. Reaction of benzoxazolones with diphosporus pentasulfide affords the corresponding 2-thione. Thiazines and oxazines can be prepared by reduction of the corresponding thiazinone or oxazinone with a reducing agent such as lithium aluminium hydride.

The amines $R^{2'}R^{4'}NH$ are available commercially or prepared conventionally. For example amines may be prepared from a bromo derivative by reaction with sodium azide in dimethylformamide (DMF), followed by hydrogenation of the azidomethyl derivative over palladium-carbon. An alternative method is to use potassium phthalimide/DMF to give the phthalimidomethyl derivative, followed by reaction with hydrazine in DCM to liberate the primary amine.

Amines where X^{2a} is CO and X^{3a} is NR^{13a} may be prepared by reacting an N-protected glycine derivative $HO_2C\text{-}X^{1a}\text{-}NH_2$ with $X^{4a}\text{-}NH_2$ by conventional coupling using eg EDC.

Conversions of $R^{1a'}$, $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$ may be carried out on the intermediates of formulae (IV) and (V) prior to their reaction to produce compounds of formula (I) in the same way as described above for conversions after their reaction.

The pharmaceutical compositions of the invention include those in a form adapted for oral, topical or parenteral use and may be used for the treatment of bacterial infection in mammals including humans.

The antibiotic compounds according to the invention may be formulated for administration in any convenient way for use in human or veterinary medicine, by analogy with other antibiotics.

The composition may be formulated for administration by any route, such as oral, topical or parenteral. The compositions may be in the form of tablets, capsules, powders, granules, lozenges, creams or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

The topical formulations of the present invention may be presented as, for instance, ointments, creams or lotions, eye ointments and eye or ear drops, impregnated dressings and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams.

The formulations may also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions. Such carriers may be present as from about 1% up to about 98% of the formulation. More usually they will form up to about 80% of the formulation.

Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrollidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives, such as suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and, if desired, conventional flavouring or colouring agents.

Suppositories will contain conventional suppository bases, e.g. cocoa-butter or other glyceride.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, water being preferred. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilised before filling into a suitable vial or ampoule and sealing.

Advantageously, agents such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. The dry lyophilized powder is then sealed in the vial and an accompanying vial of water for injection may be supplied to reconstitute the liquid prior to use. Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compositions may contain from 0.1% by weight, preferably from 10-60% by weight, of the active material, depending on the method of administration. Where the compositions comprise dosage units, each unit will preferably contain from 50-500 mg of the active ingredient. The dosage as employed for adult human treatment will preferably range from 100 to 3000 mg per day, for instance 1500 mg per day depending on the route and frequency of administration. Such a dosage corresponds to 1.5 to 50 mg/kg per day. Suitably the dosage is from 5 to 20 mg/kg per day.

No toxicological effects are indicated when a compound of formula (I) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof is administered in the above-mentioned dosage range.

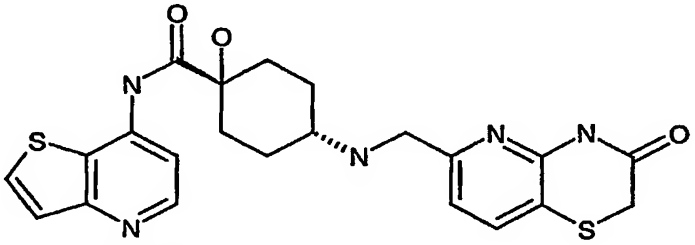
The compound of formula (I) may be the sole therapeutic agent in the compositions of the invention or a combination with other antibiotics or with a β-lactamase inhibitor may be employed.

Compounds of formula (I) are active against a wide range of organisms including both Gram-negative and Gram-positive organisms.

The following examples illustrate the preparation of certain compounds of formula (I) and the activity of certain compounds of formula (I) against various bacterial organisms.

Examples

Example 1 1-Hydroxy-*t*-4-[(3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazin-6-ylmethyl)-amino]-*r*-cyclohexanecarboxylic acid thieno[3,2-b]pyridin-7-ylamide dihydrochloride



(a) 2-Acetoxycyclohex-3-enecarboxylic acid butyl ester

1-Acetoxy-1,3-butadiene (30.1 g, 0.268 mol) was dissolved in toluene (20 ml). To this was added butyl acrylate (37.9 ml, 0.265 mol) and hydroquinone (0.14 g). The colourless solution was heated at 120°C for 26 hours under argon. More 1-acetoxy-1,3-butadiene (10.6 g, 0.095 mol) in toluene (2 ml) was then added, and heating continued for a further 68 hours. The solution was cooled then evaporated *in vacuo* to give a viscous yellow oil (69 g), which was used without further purification.

δH ($CDCl_3$) 0.91-0.95 (3H, m), 1.3-2.2 (11H, m), 2.6-2.72 (1H, m), 4.01-4.16 (2H, m), and 5.48-6.07 (3H, m).

(b) Cyclohexa-1,3-dienecarboxylic acid butyl ester

Crude butyl ester (a) (55.25 g, max 0.207 mol) was dissolved in dry tetrahydrofuran (320 ml) and cooled in an ice/salt bath. To this was added slowly, over 1 hour, potassium t-butoxide in tetrahydrofuran (1 M, 220 ml, 0.22 mol). After 0.5 hour water and petroleum ether were added and the mixture filtered quickly through kieselguhr. The phases were separated and the aqueous extracted with more petroleum ether (x2). The combined organic extracts were washed with brine, dried and evaporated to give a mobile orange oil (31.85 g, 86%), which was used immediately without further purification.

δH ($CDCl_3$) 0.93-0.99 (3H, m), 1.3-1.7 (4H, m), 2.2-2.5 (4H, m), 4.1-4.2 (2H, m), 6.0-6.2 (2H, m), and 6.95-7.02 (1H, m).

(c) 2-Oxa-3-aza-bicyclo[2.2.2]oct-5-ene-1,3-dicarboxylic acid 3-benzyl ester 1-butyl ester

Crude butyl ester (b) (31.84 g, max 0.176 mol) was dissolved in dichloromethane (300 ml). To this was added N-hydroxy carbamic acid benzyl ester (30.9 g, 0.185 mol). This solution was cooled in an ice/salt bath then a solution of tetrabutylammonium periodate (80.1 g, 0.185 mol) in dichloromethane (100 ml) was added dropwise over 1 hour. After stirring for a further 1 hour, with cooling, the mixture was reduced to a small

volume *in vacuo* then stirred vigorously while adding diethyl ether (1 litre). The mixture was filtered washing well with diethyl ether. The filtrate was then washed with aqueous sodium bisulphite (x2), and brine, dried and evaporated to give a brown oil. This residue was purified by chromatography on silica gel, eluting with 25 – 28% diethyl ether in petroleum ether, to give a viscous pale orange oil (42.41 g, ~69%) (contaminated with a little benzyl alcohol).
δH (CDCl3) 0.94 (3H, t), 1.35-1.75 (6H, m), 2.15-2.4 (2H, m), 4.2-4.35 (2H, m), 4.84-4.89 (1H, m), 5.12-5.20 (2H, m), 6.59-6.71 (2H, m), and 7.28-7.39 (5H, m).

(d) 2-Oxa-3-aza-bicyclo[2.2.2]oct-5-ene-1,3-dicarboxylic acid 3-benzyl ester

To a solution of di-ester (c) (42.13 g, 0.122 mol) in 1,4-dioxane (250 ml) was added aqueous sodium hydroxide solution (0.5 M, 250 ml, 0.125 mol). The mixture was stirred for 1 hour then washed with diethyl ether (x3). The aqueous phase was adjusted to pH2 with 5 M hydrochloric acid, and extracted with ethyl acetate (x3). The combined organic extracts were washed with brine, dried and evaporated to give a cream solid (29.53 g, 84%).
δH ($CDCl_3/CD_3OD$) 1.53-1.79 (2H, m), 2.13-2.39 (2H, m), 4.82-4.89 (1H, m), 5.11-5.23 (2H, m), 6.57-6.69 (2H, m), and 7.3-7.4 (5H, m).

(e) 1-Carbamoyl-2-oxa-3-aza-bicyclo[2.2.2]oct-5-ene-3-carboxylic acid benzyl ester

The benzyl ester (d) (12.0 g, 41.5 mmol) and 1-hydroxy-7-azabenzotriazole (6.26 g, 46 mmol) were dissolved in DMF (100 ml) then 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (8.79 g, 46 mmol) added. After stirring for 5 minutes ammonium hydrogen carbonate (8.22 g, 104 mmol) was added. Four further small portions of ammonium hydrogen carbonate were added over the next 7 hours. The mixture was then stirred overnight, diluted with water and extracted with ethyl acetate (x4). The combined organic extracts were washed with 5% aqueous citric acid then brine, dried and evaporated to give an off-white solid (9.9 g, 83%).
MS (+ve ion electrospray) m/e 289 (MH+).

(f) (4-Carbamoyl-*r*-4-hydroxy-*c*-cyclohexyl)-carbamic acid *tert* butyl ester

The benzyl ester (e) (9.75 g, 33.8 mmol) was dissolved in 1,4-dioxane (150 ml) and water (60 ml) and hydrogenated over 10% palladium on carbon (50% aqueous paste, 3.3 g) at 40°C and 55 psi for 68 hours. More catalyst (2 g) was added after 4 hours. The mixture was then filtered through kieselguhr, washing well with 1,4-dioxane and water. To this solution was added 2 N sodium hydroxide (25 ml, 50 mmol) followed by a solution of di-*tert*-butyl dicarbonate (11.12 g, 51 mmol) in 1,4-dioxane (10 ml). The

reaction mixture was stirred for 5 hours then reduced in volume *in vacuo*, before extracting with ethyl acetate (x5). The combined organic extracts were dried and evaporated to give a white solid (5.96 g), which was chromatographed on silica (400 g). Elution with 0-7% methanol in dichloromethane gave a white powder (5.52 g, 63%) δH (d_6-DMSO) 1.3-1.76 (17H, m), 3.17 (1H, br s), 4.95 (1H, s), 6.71 (1H, d), 7.0 (1H, s), and 7.14 (1H, s).

(g) Methyl 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylate

A solution of ethyl 2-mercaptoacetate (1.473 ml) in DMF (48 ml) was ice-cooled and treated with sodium hydride (540 mg of a 60% dispersion in oil). After 1 hour methyl 6-amino-5-bromopyridine-2-carboxylate (3 g) (T.R. Kelly and F. Lang, *J. Org. Chem. 61*, 1996, 4623-4633) was added and the mixture stirred for 16 hours at room temperature. The solution was diluted with EtOAc (1 litre), washed with water (3 x 300ml), dried and evaporated to about 10 ml. The white solid was filtered off and washed with a little EtOAc to the ester (0.95g).
MS (APCI$^-$) *m/z* 223 ([M-H]$^-$, 100%)

(h) 3-Oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid

A solution of ester (g) (788 mg) in dioxan (120 ml)/water (30 ml) was treated dropwise over 2 hours with 0.5M NaOH solution (8 ml) and stirred overnight. After evaporation to approx. 3 ml, water (5ml) was added and 2N HCl to pH4. The precipitated solid was filtered off, washed with a small volume of water and dried under vacuum to give a solid (636mg).
MS (APCI$^-$) *m/z* 209 ([M-H]$^-$, 5%), 165([M-COOH]$^-$, 100%)

(i) 6-Hydroxymethyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine

A solution of the carboxylic acid (h) (500mg) in THF (24ml) with triethylamine (0.396ml) was cooled to -10°C and isobutyl chloroformate (0.339ml) added. After 20 minutes the suspension was filtered through kieselguhr into an ice-cooled solution of sodium borohydride (272 mg) in water (8 ml), the mixture stirred 30 minutes and the pH reduced to 7 with dilute HCl. The solvent was evaporated and the residue triturated under water. The product was filtered and dried under vacuum to give a white solid (346mg).
MS (APCI$^-$) *m/z* 195 ([M-H]$^-$, 50%), 165(100%)

(j) 3-Oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxaldehyde

A solution of the alcohol (i) (330 mg) in dichloromethane (30 ml)/THF (30 ml) was treated with manganese dioxide (730 mg) and stirred at room temperature. Further

manganese dioxide was added after 1 hour (730 mg) and 16 hours (300 mg). After a total of 20 hours the mixture was filtered through kieselguhr and the filtrate evaporated. The product was triturated with EtOAc/hexane (1:1) and collected to give a solid (180mg).

(k) 7-Bromo-thieno[3,2-b]pyridine

A suspension of 4H-thieno[3,2-b]pyridin-4-one (5g, 33.1 mmol) in DMF (35 ml) was treated at 0°Cwith phosphorous tribromide (3.1 ml, 39.7 mmol). After 1 hour the mixture was added to a mixture of ice/saturated aqueous sodium hydrogen carbonate solution. Filtration and drying in vacuo afforded a pale yellow solid (5.9g, 83%).

(l) [4-Hydroxy-4-(thieno[3,2-b]pyridin-7-ylcarbamoyl)-cyclohexyl]-carbamic acid tert-butyl ester

A mixture of the amide (f) (387 mg, 1.5 mmol), cesium carbonate (0.61 g), tris(dibenzylideneacetone)dipalladium(0) (27 mg), and rac-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (56 mg) in dry dioxan (12 ml) under argon was sonicated for 10 minutes. Bromide (k) (321 mg, 1.5 mmol) was added, and the mixture was stirred and heated at 100°C for 24 hours under argon. The mixture was cooled, centrifuged, then the supernatant evaporated and chromatographed on silica gel, eluting with dichloromethane, then 0-10% methanol in ethyl acetate affording a solid (495 mg, 84%).
MS (+ve ion electrospray) m/z 392 (MH+).

(m) 4-Amino-1-hydroxy-cyclohexanecarboxylic acid thieno[3,2-b]pyridin-7-ylamide

A solution of carbamate (l) (490 mg, 1.25 mmol) in dichloromethane (7.5 ml) was treated with trifluoroacetic acid (7.5 ml). After 2 hours the mixture was evaporated, azeotroping with toluene.The residue was partitioned between ethyl acetate and saturated aqueous sodium hydrogen carbonate solution. The organic extract was dried and evaporated affording a yellow solid (167 mg, 45%).
MS (+ve ion electrospray) m/z 292 (MH+).

(n) Title compound

A mixture of amine (m) (167 mg, 0.57 mmol) and aldehyde (j) (111 mg, 0.57 mmol) in methanol/DMF/acetic acid (7 ml/7 ml/0.7 ml) was treated with 3A molecular sieves and heated at 80°C for 1.5 hours. The mixture was allowed to cool to room temperature then sodium cyanoborohydride (72 mg, 1.15 mmol) was addded. The mixture was stirred at room temperature overnight, acidified briefly with 5M hydrochloric acid (0.5 ml) then partitioned between ethyl acetate and saturated aqueous sodium hydrogen carbonate solution. The organic extract was dried and evaporated affording a yellow

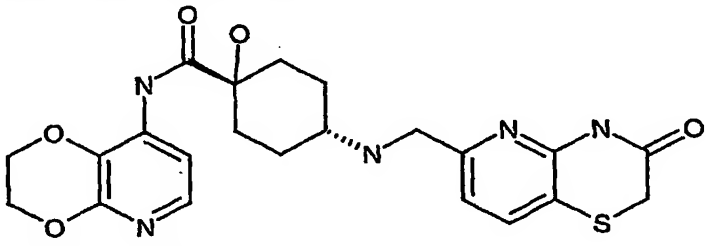
solid. The residue was chromatographed on silica eluting with a 0-20% methanol in ethyl acetate gradient affording the free base of the title compound as a white solid (171 mg, 71%).

^{1}H NMR δ(CD_3OD) 8.55 (1H, d), 7.96 (2H, m), 7.70 (1H, d), 7.50 (1H, d), 7.05 (1H, d), 3.90 (2H, s), 3.50 (2H, s), 2.70 (1H, m), 2.10-1.60 (8H, m)

MS (+ve ion electrospray) m/z 470 (MH+).

This material was dissolved in chloroform/methanol (3 ml/3 ml) and treated with 1M HCl in ether (2 ml) with vigorous shaking. The resulting white solid was isolated by centrifugation and dried under vacuum to provide the title compound (119 mg).

Example 2 1-Hydroxy-*t*-4-[(3-oxo-3,4-dihydro-2H -pyrido[3,2-b][1,4]thiazin-6-ylmethyl)-amino]-*r*-cyclohexanecarboxylic acid (2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-8-yl)-amide dihydrochloride



(a) 8-Bromo-2,3-dihydro-[1,4]dioxino[2,3-b]pyridine

A solution of 2,3-dihydro-[1,4]dioxino[2,3-b]pyridine (prepared by the method of H. Neunhoffer *et al*, Chem., Ber., 1990, **123** (12), 2453) (1.37g, 10 mmol) in tetrahydrofuran (20 ml) under argon at –78°C was treated over 15 minutes with a solution of n-butyl lithium (20 mmol) in tetrahydrofuran (8 ml). After 30 minutes a solution of 1,2-dibromo-1,1,2,2-tetrafluoro-ethane (2.6g, 10 mmol) in tetrahydrofuran (10 ml) was added dropwise over 5 minutes. After a further 30 minutes the cooling bath was removed and saturated aqueous ammonium chloride (20ml) and ether (20 ml) were added. The mixture was allowed to warm to room temperature then partitioned between ether/water. The organic extract was washed with half-saturated brine, dried and evaporated. The residue was chromatographed on silica eluting with a 0-30% gradient of ethyl acetate in dichloromethane affording a yellow solid (1.1g, 51%).

MS (+ve ion electrospray) m/z 217 (MH+).

(b) [4-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-8-ylcarbamoyl)-4-hydroxy-cyclohexyl]-carbamic acid tert-butyl ester

This was prepared from bromide (a) (432 mg) and amide (1f) (516 mg) by the procedure of Example (1l) affording a yellow solid after chromatography (105 mg, 13%).

MS (+ve ion electrospray) m/z 394 (MH+).

(c) 4-Amino-1-hydroxy-cyclohexanecarboxylic acid (2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-8-yl)-amide

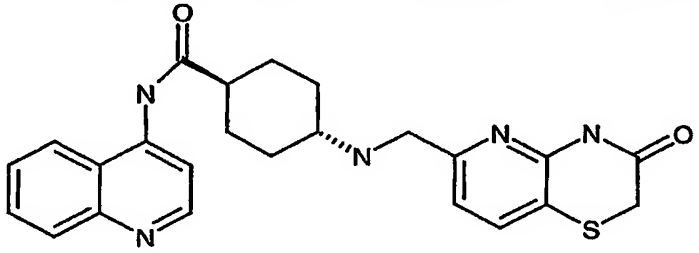
This was prepared from carbamate (b) (105 mg) by the procedure of Example (1m) with the exception that the crude material was subjected to chromatography on silica eluting with a 0-30% methanol in ethyl acetate gradient affording an oil (25 mg, 32%).
MS (+ve ion electrospray) m/z 394 (MH+).

(d) Title compound

This was prepared from amine (c) (25 mg) and aldehyde (1j) (16 mg) according to the procedure of Example (1n) affording the free base of the title compound as a white solid (4 mg, 10%).
^{1}H NMR δ(CD_3OD) 7.95 (1H, d), 7.75 (1H, d), 7.65 (1H, d), 7.07 (1H, d), 4.45 (2H, m), 4.38 (2H, m), 4.10 (2H, s), 3.52 (2H, s), 2.80 (1H, m), 2.10-1.60 (8H, m)
MS (+ve ion electrospray) m/z 472 (MH+).

The free base was converted into the dihydrochloride salt by the procedure of Example 1 affording a white solid (5 mg).

Example 3 trans-4-[(3-Oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazin-6-ylmethyl)-amino]-cyclohexanecarboxylic acid quinolin-4-ylamide dihydrochloride



(a) trans-(4-Carbamoyl-cyclohexyl)-carbamic acid tert-butyl ester

A solution of trans-4-tert-butoxycarbonylamino-cyclohexanecarboxylic acid (15g, 61.7 mmol) and 1-hydroxysuccinimide (76g, 61.7 mmol) in ethyl acetate (200 ml) was treated with a solution of dicyclohexylcarbodiimide (12.7g, 61.7 mmol) in ethyl acetate (50 ml). After stirring overnight the mixture was filtered and evaporated affording a yellow solid. This was redissolved in tetrahydrofuran (300 ml) and treated gaseous ammonia was bubbled through the solution for 15 minutes. Filtration afforded a white solid which was stirred in water (200 ml) for 1 hour. Filtration and drying afforded a white solid (11.3g, 76%).
MS (+ve ion electrospray) m/z 243 (MH^+).

(b) trans-[4-(Quinolin-4-ylcarbamoyl)-cyclohexyl]-carbamic acid tert-butyl ester

This was prepared from 4-chloroquinoline (0.49g) and amide (a) (0.73g) according to the procedure of Example (11) affording a white solid (0.66g, 60%).
MS (+ve ion electrospray) m/z 370 (MH^+).

(c) trans-4-Amino-cyclohexanecarboxylic acid quinolin-4-ylamide

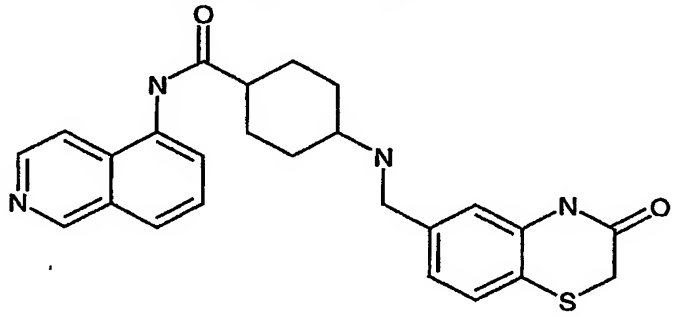
This was prepared from carbamate (b) (0.65g) according to the procedure of Example (1m) affording a white solid (280 mg, 58%).
MS (+ve ion electrospray) m/z 270 (MH^+).

(d) Title compound

This was prepared from amine (c) (220 mg) and aldehyde (1j) (160 mg) according to the procedure of Example (1n) affording the free base of the title compound as a white foam (104 mg, 27%).
^1H NMR δ($CDCl_3$) 9.30 (1H, bs), 9.00 (1H, bs), 8.80 (1H, d), 8.20 (1H, d), 8.15 (1H, d), 8.05 (1H, d), 7.70 (1H, t), 7.60-7.50 (2H, m), 6.95 (1H, d), 3.90 (2H, s), 3.45 (2H, s), 2.70 (1H, m), 2.20-2.00 (4H, m), 1.80-1.70 (2H, m), 1.40-1.30 (2H, m)
MS (+ve ion electrospray) m/z 448 (MH+).

The free base was converted into the dihydrochloride salt by the procedure of Example 1 affording a white solid (110 mg).

Example 4 trans-4-[(3-Oxo-3,4-dihydro-2H-benzo[1,4]thiazin-6-ylmethyl)-amino]-cyclohexanecarboxylic acid isoquinolin-5-ylamide



(a) 3-Oxo-3,4-dihydro-2H-benzo[1,4]thiazine-6-carboxylic acid

3-Oxo-3,4-dihydro-2H-benzo[1,4]thiazine-6-carboxylic acid methyl ester (6.74 g) was suspended in tetrahydrofuran (100 ml) and 2M sodium hydroxide (30 ml) was added followed by water (20 ml). The solution was stirred for 2.5 hours, evaporated to half volume and acidified with 2M hydrochloric acid. The product was collected, washed with water and dried *in vacuo*, to give a white solid (6.2 g).
MS (-ve ion electrospray) *m/z* 208 $(M-H)^-$

(b) 6-Hydroxymethyl-4H-benzo[1,4]thiazin-3-one

The acid (a) in tetrahydrofuran (50 ml) and triethylamine (4.7 ml) was cooled to 0°C and *iso*butylchloroformate (4.02 ml) was added dropwise and the solution was stirred at 0°C for 2 hours, when it was filtered into a stirred solution of sodium borohydride (3.14 g) in ice/water (50 ml). The mixture was stirred at 0°C for 1 hour and allowed to warm to room temperature. It was acidified with 2M hydrochloric acid, evaporated to half volume, and the resulting product was collected, washed with water and dried *in vacuo*, to give a white solid (4.5 g).

MS (-ve ion electrospray) *m/z* 194 $(M-H)^-$

(c) 3-Oxo-3,4-dihydro-2H-benzo[1,4]thiazine-6-carboxaldehyde

A stirred solution of the alcohol (b) (3.5 g) in chloroform (150 ml) and tetrahydrofuran (300 ml) was treated with manganese dioxide (7.8 g) for 18 hours and was filtered and evaporated to give a white solid (2.5 g).

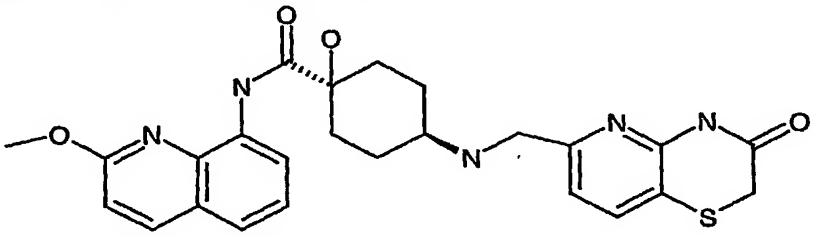
MS (-ve ion electrospray) *m/z* 194 $(M-H)^-$

(d) Title compound

This was prepared from trifluoromethane sulphonic acid-isoquinolin-5-yl ester (prepared as in D. Ortwine et al, J. Med. Chem., 1992, 35 (8), 1345) by the same methodology as in Example 3, with the exception that aldehyde (c) was used in the final reductive alkylation step.

LC/MS: (ES) *m/z* 447 $(M+H)^+$.

Example 5 1-Hydroxy-*t*-4-[(3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazin-6-ylmethyl)-amino]-*r*-cyclohexanecarboxylic acid (2-methoxy-quinolin-8-yl)-amide



(a) 8-Benzyloxyquinolin-2-ol

This was prepared by a slight modification of the procedure of Guo *et al*, Tet Lett, 1999, **40**, 6999. To a stirred solution of 2,8-quinolinediol (4.97 g,30.84 mmol) and 1,8-diazabicylo[5.4.0]undec-7-ene (DBU) (40.2 mmol, 6 mL) in isopropyl alcohol (60 mL) was added benzyl bromide (3.7mL,30.84 mmol). The solution was heated at reflux overnight. The reaction mixture was allowed to cool and then concentrated *in vacuo*. The resulting residue was diluted with CH_2Cl_2 and washed with 0.5 N NaOH, 10% HCl

and water and dried over Na_2SO_4. Concentration provided 6 g (77%) of a tan solid , which was used without further purification.
LC/MS: (ES) *m/z* 252 $(M+H)^+$.

(b) 8-Benzyloxy-2-methoxyquinoline

8-Benzyloxyquinolin-2-ol (a) (6 g, 23.9 mmol) was added to $POCl_3$ (45 mL) and heated with stirring at 80 °C for 10 hours. The reaction was allowed to cool to room temperature and the excess $POCl_3$ was decomposed by slowly pouring the mixture into water at 30 °C. The product was then extracted into toluene and the combined organic layers were washed with saturated aqueous $NaHCO_3$ and dried over $MgSO_4$. Concentration provided 6.9 g of a colorless oil which was dissolved in toluene (10mL) and added to a stirred 25 wt% solution of NaOMe in MeOH (50 mL). The reaction solution was heated overnight at 70 °C. After cooling to room temperature, the reaction solution was poured onto ice and extracted with toluene. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give a colorless oil (6.14 g, 92%).
LC/MS: (ES) *m/z* 266 $(M+H)^+$.

(c) 1,1,1-Trifluoromethanesulfonic acid 2-methoxyquinolin-8-yl ester

8-Benzyloxy-2-methoxyquinoline (b) (6.14 g, 23 mmol) was dissolved in EtOH (50 mL) and treated with 10% Pd/C (600 mg). The reaction mixture was hydrogenated under an H_2 atmosphere (20 psi) in a Parr shaker apparatus for 3.5 hours. The reaction was filtered and concentrated to give 3.8 g (96%) of a colorless oil. This was dissolved in DMF (40 mL) and treated with triethylamine (3.6 mL, 25.8 mmol) and N-phenyltrifluoromethanesulfonimide (8.54 g, 23.9 mmol). The reaction mixture was heated with stirring at 40 °C for 8 hours. Upon cooling to room temperature, aqueous K_2CO_3 solution was added and the product was extracted into CH_2Cl_2. The combined organic extracts were washed with water (5x75 mL), dried (Na_2SO_4) and concentrated to give 6.8 g (100%) of a light tan crystalline solid.
LC/MS: (ES) *m/z* 308 $(M+H)^+$.

(d) [*r*-4-Hydroxy-4-(2-methoxyquinolin-8-ylcarbamoyl)-*c*-cyclohexyl]carbamic acid *tert*-butyl ester

A flask containing amide (1f) (847mg, 3.28 mmol), rac-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (133mg, 0.21 mmol) and Cs_2CO_3 (1.33 g, 4.1 mmol) in dioxane (30 mL) was flushed with N_2. To this was added $Pd_2(dba)_3$ (63 mg, 0.07 mmol) and the reaction solution was sonicated for 10 min as the color changed from purple to brown. A solution of 1,1,1-trifluoromethanesulfonic acid 2-methoxyquinolin-8-

yl ester (c) (1.09 g, 3.54 mmol) in dioxane (15 mL) was then added. The reaction mixture was heated with stirring at 100 °C for 18 hours. Upon cooling to room temperature, the reaction mixture was filtered through celite® and concentrated. The product was purified on an ISCO Combiflash® automated column chromatography unit (silica, 0% to 10% MeOH/EtOAc) to provide 846 mg (65%) of the desired product as a pale yellow solid.
LC/MS: (ES) *m/z* 416 $(M+H)^+$.

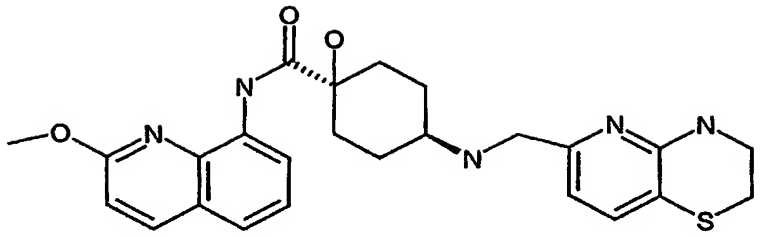
(e) *t*-4-Amino-1-hydroxy-*r*-cyclohexanecarboxylic acid (2-methoxyquinolin-8-yl)amide dihydrochloride

A solution of (d) (134 mg, 0.32 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C. To this was added 4M HCl/dioxane (1.57 mL, 6.28 mmol) in one portion and the reaction solution was stirred at room temperature for 5 hours. The reaction solution was filtered and the solids washed with ether and dried under vacuum to provide a pale yellow solid (65 mg).
LC/MS: (ES) *m/z* 316 $(M+H)^+$.

(f) Title compound

The dihydrochloride salt (e) (55 mg, 0.14 mmol), aldehyde (1j) (50 mg, 0.25 mmol), triethylamine (0.10 mL, 0.72 mmol), DMF (0.5 mL), HOAc (0.5 mL) and MeOH (7 mL) were combined together and stirred in the presence of 3Å molecular sieves for 3 hours at 80 °C and then at room temperature overnight. $NaCNBH_3$ (54 mg, 0.86 mmol) was added and the reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was diluted with 10% MeOH/$CHCl_3$ and aq Na_2CO_3 was added. The aqueous layer was extracted with 10% MeOH/$CHCl_3$ (4X) and the combined organic extracts were dried (Na_2SO_4). The product was purified on an ISCO Combiflash® automated column chromatography unit (silica, 0% to 10% MeOH/$CHCl_3$) to provide 31 mg (45%) of the title compound as a white solid.
^1H NMR (400 MHz) δ 1.80-2.10 (m, 8H), 3.10 (m, 1H), 3.51 (s, 2H), 4.09 (s, 3H), 4.18 (s, 2H), 6.95-6.98 (d, 1H), 7.04-7.07 (d, 1H), 7.30-7.35 (t, 1H), 7.48-7.50 (d, 1H), 7.73-7.75 (d, 1H), 8.09-8.11 (d, 1H), 8.56-8.58 (d, 1H).
LC/MS: (ES) *m/z* 494 $(M+H)^+$.

Example 6 4-[(3,4-Dihydro-2H-pyrido[3,2-b][1,4]thiazin-6-ylmethyl)-amino]-1-hydroxy-cyclohexanecarboxylic acid (2-methoxy-quinolin-8-yl)-amide



(a) (3,4-Dihydro-2H-pyrido[3,2-b][1,4]thiazine-6-yl)-methanol

A solution of methyl 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazine-6-carboxylate (1g) (1.0 g) in dry tetrahydrofuran (170 ml) was treated with a 1M solution of lithium aluminium hydride in ether (14 ml) and the mixture was heated under reflux for 18 hours. It was cooled and a slight excess of 2N sodium hydroxide was added followed by chloroform and anhydrous sodium sulphate and the mixture was stirred for 30 minutes and filtered. The solution was evaporated to dryness to give a semi-solid (0.482 g).
MS (APCI$^+$) *m/z* 183 (MH^+).

(b) 3,4-Dihydro-2H-pyrido[3,2-b][1,4]thiazine-6-carboxaldehyde

The alcohol (a) (0.482 g) in dry dichloromethane (50 ml) was stirred with manganese dioxide (1.2 g) for 18 hours and the mixture was filtered. The filtrate was evaporated and chomatographed on silica gel, eluting with methanol-dichloromethane (1:50) to afford a yellow solid (0.24 g) .
MS (APCI$^+$) *m/z* 181 (MH^+).

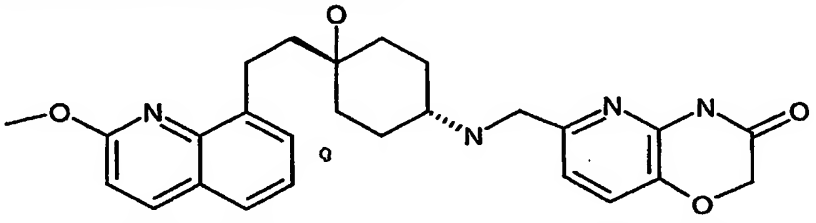
(c) Title compound

Dihydrochloride salt (5e) (65 mg, 0.16 mmol), aldehyde (b) (75 mg, 0.42 mmol), triethylamine (0.15 mL, 1.08 mmol), DMF (0.5 mL), HOAc (0.5 mL) and MeOH (7 mL) were combined together and stirred in the presence of 3Å molecular sieves for 3 hours at 80 °C and then at room temperature overnight. $NaCNBH_3$ (47 mg, 0.75 mmol) was added and the reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was diluted with 10% MeOH/$CHCl_3$ and aq Na_2CO_3 was added. The aqueous layer was extracted with 10% MeOH/$CHCl_3$ (4X) and the combined organic extracts were dried (Na_2SO_4). The product was purified on an ISCO Combiflash® automated column chromatography unit (silica, 0% to 10% MeOH/$CHCl_3$) to provide 70 mg (92%) of the title compound as a pale yellow solid.

^1H NMR (400 MHz) δ 1.77-2.08 (m, 8H), 2.71 (m, 1H), 2.89-2.91 (m, 2H), 3.66-3.67 (m, 2H), 3.76 (s, 2H), 4.00 (s, 3H), 5.38 (br s, 1H), 6.40-6.42 (d, 1H), 6.81-6.83 (d, 1H), 7.08-7.10 (d, 1H), 7.24-7.28 (t, 1H), 7.33-7.35 (d, 1H), 7.87-7.89 (d, 1H), 8.61-8.63 (d,. 1H) 10.92 (s, 1H).

LC/MS: (ES) *m/z* 480 $(M+H)^+$.

Example 7 6-({4-Hydroxy-4-[2-(2-methoxy-quinolin-8-yl)-ethyl]-cyclohexylamino}-methyl)-4H-pyrido[3,2-b][1,4]oxazin-3-one



(a) (*r*-4-Hydroxy-4-trimethylsilanyl-*c*-cyclohexyl)carbamic acid *tert*-butyl ester

A stirred solution of trimethylsilyl acetylene at -78 °C(4.14 g, 0.042 mol) in THF (60 mL) was treated with n-butyl lithium (29 mL, 0.042 mol; 1.6 M solution in THF). The resulting mixture was stirred at -78 °C for 15 min. A solution of N-4-Boc-aminocyclohexanone (3 g, 0.014 mol) in THF (120 mL) was added dropwise over a period of 30 min. The resulting mixture was stirred at -78 °C for 1 hour and then allowed to slowly warm to room temperature over 1 hour. The reaction was quenched with a saturated aqueous solution of ammonium chloride, diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ solution, H_2O, and saturated aqueous NaCl solution. The organic extract was dried over $MgSO_4$ and concentrated to yield the title compound as an off-white foam (4.38 g, 100%).
MS (ES) *m/z* 312 $(M + H)^+$.

(b) (*t*-4-Ethynyl-4-hydroxy-*r*-cyclohexyl)carbamic acid *tert*-butyl ester

A solution of (a) (4.38 g, 0.014 mol) in MeOH (50 mL) was treated with K_2CO_3 (5.83 g, 0.42 mol) and stirred at room temperature for 3 hours. The solvent was removed *in vacuo* and the residue was partitioned between EtOAc and aqueous NaCl, and the organic layer was dried ($MgSO_4$) and concentrated to yield an oil (2.7 g, 89%).
MS (ES) *m/z* 240 $(M + H)^+$.

(c) [*r*-4-Hydroxy-4-(2-methoxyquinoline-8-ylethynyl)-*c*-cyclohexyl]carbamic acid *tert*-butyl ester

A solution of (b) (500 mg, 2.09 mmol) and triflate (5c) (656 mg, 2.13 mmol) in a 1:1 mixture of triethylamine and DMF (10 mL total volume) was treated with $(Ph_3P)_2PdCl_2$ (60 mg; 4% mol) and CuI (32 mg, 8% mol). The resulting mixture was heated with stirring at 70 °C for 24 hours. The solvent was removed under reduced pressure and the residue was partitioned between CH_2Cl_2 and aqueous NaCl, and the organic layer was dried ($MgSO_4$), and concentrated *in vacuo*. The resulting oil was

purified by flash column chromatography on silica gel (gradient: 20-50% EtOAc/hexane) to afford a yellow foam (635 mg , 82%). LC/MS: MS (ES) *m/z* 397 $(M + H)^+$.

(d) {*r*-4-Hydroxy-4-[2-(2-methoxyquinolin-8-yl)ethyl]-*c*-cyclohexyl}carbamic acid *tert*-butyl ester

A solution of (c) (635 mg, 1.6 mmol) in MeOH (10 mL) was treated with 10% Pd/C (65mg) and hydrogenated in a Parr bottle for 6 h at 40 psi. The solution was filtered through a plug of celite®, and the filter pad was washed with MeOH. The filtrate was concentrated to yield the title compound (608 mg, 95%) as a light yellow foam.
LC/MS: (ES) *m/z* 401 $(M + H)^+$.

(e) *t*-4-Amino-*r*-1-[2-(2-methoxyquinolin-8-yl)ethyl]cyclohexanol trifluoroacetate

A stirred solution of (d) (600 mg, 1.5 mmol) in CH_2Cl_2 (5 mL) was treated with trifluoroacetic acid (1.16 mL, 15 mmol). The solution was allowed to stir for 1 hour at room temperature and then concentrated under reduced pressure. MeOH was added and the solution was again concentrated to afford a solid (1.06 g)
LC/MS: (ES) *m/z* 301 $(M + H)^+$.

(f) 2-Bromo-5-hydroxy-6-nitropyridine

3-Hydroxy-2-nitropyridine (20 g, 0.143 mole) was dissolved in methanol (400 mL) and a solution of 25% sodium methoxide in methanol (33 mL, 0.13 mole) was added at room temperature. The mixture was stirred for 30 min, then was cooled to 0 °C, and bromine (7.2 mL, 0.14 mole) was added slowly. The reaction was then stirred at 0 °C for 30 min, then was quenched with glacial AcOH (2.5 mL). The solvent was removed *in vacuo* to afford material (30 g, 96%), which was used without further purification.
MS (ES) *m/z* 219.0 $(M + H)^+$.

(g) Ethyl (6-bromo-2-nitro-pyridin-3-yloxy)acetate

The hydroxypyridine (f) (30 g, 0.14 mole) was suspended in acetone (200 mL), and potassium carbonate (39 g, 0.28 mole) was added, followed by ethyl bromoacetate (15.7 mL, 0.14 mmole). The reaction was heated at reflux for 10 hr, then was cooled to room temperature and diluted with Et_2O. The precipitate was removed by suction filtration, and the filtrate was concentrated *in vacuo* to afford material (38 g, 89%), which was used without further purification.
MS (ES) *m/z* 305.0 $(M + H)^+$.

(h) 6-Bromo-4*H*-pyrido[3,2-b][1,4]oxazin-3-one

The nitropyridine (g) (38 g, 0.125 mole) was dissolved in glacial AcOH (150 mL), and iron powder (20 g, 0.36 mole) was added. The mixture was mechanically stirred and heated at 90 °C for 5 hr, then was cooled to room temperature and diluted with EtOAc (300 mL). The mixture was filtered through a pad of silica gel and the filtrate was concentrated *in vacuo* and the residue recrystallized from MeOH (15 g, 52%).
MS (ES) *m/z* 229.0 $(M + H)^+$.

(i) 6-((*E*)-Styryl)-4*H*-pyrido[3,2-*b*][1,4]oxazin-3-one

The bromopyridine (h) (6.0 g, 26.3 mmole) and *trans*-2-phenylvinylboronic acid (3.9 g, 26.3 mmole) were dissolved in 1,4-dioxane (150 mL) and the solution was degassed with argon. $(Ph_3P)_4Pd$ (230 mg, 0.2 mmole) was added, followed by a solution of potassium carbonate (6.9 g, 50 mmole) in H_2O (20 mL). The reaction was heated at reflux under argon overnight, then was cooled to room temperature and diluted with EtOAc (200 mL). The solution was washed sequentially with H_2O and brine, dried (Na_2SO_4), and concentrated *in vacuo*. The solid residue was purified by flash chromatography on silica gel (5-10% EtOAc/$CHCl_3$) to afford a solid (2.5 g, 38%).
MS (ES) *m/z* 253.0 $(M + H)^+$.

(j) 3-Oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxaldehyde

The pyridine (i) (1.2 g, 4.8 mmole) was dissolved in CH_2Cl_2 (200 mL) and the solution was cooled to -78 °C. Ozone was bubbled through the solution with stirring until a pale blue color appeared, then the excess ozone was removed by bubbling oxygen through the solution for 15 min. Dimethylsulfide (1.76 mL, 24 mmole) was added to the solution, and the reaction was stirred at -78 °C for 3 hr, then at room temperature overnight. The solvent was removed *in vacuo*, and the residue was triturated with Et_2O (50 mL). The collected solid was washed with additional Et_2O and dried to afford a solid (700 mg, 82%).
MS (ES) *m/z* 179.0 $(M + H)^+$.

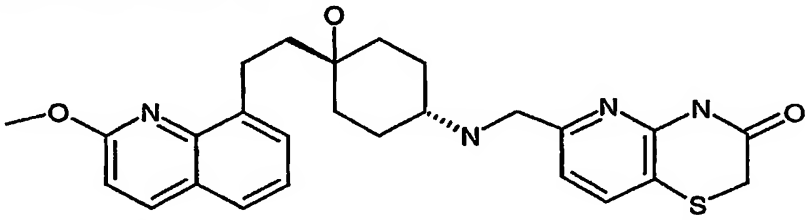
(k) Title compound

Amine trifluoroacetate (e) (270 mg, 0.51 mmol) was added to a stirred solution of aldehyde (j) (100 mg, 0.561 mmol) dissolved in DMF (3 mL) and MeOH (2 mL). $NaHCO_3$ (214 mg, 2.55 mmol) was added to the reaction mixture and the solution was allowed to stir at 80 °C for 16 hours. The solution was cooled to 0 °C and sodium borohydride (0.042 g, 1.12 mmol) was added. The reaction was stirred at ambient temperature for 4 hours. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with water (2X) and brine, dried (Na_2SO_4) and

concentrated. Purification using flash column chromatography on silica gel (90:10:1 $CHCl_3$/MeOH/NH_4OH) provided the title compound (92 mg, 39%) as a light yellow foam.

^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, 1H); 7.55 (d, 1H); 7.48 (d, 1H); 7.29 (t, 1H); 7.18 (d, 1H); 6.93 (d, 1H); 6.88 (d, 1H); 4.61 (s, 2H); 4.06 (s, 3H); 3.86 (s, 2H); 3.25 (m, 2H); 2.52 (m, 1H); 1.89 (m, 2H); 1.79 (m, 2H); 1.76 (m, 2H); 1.59 (m, 2H); 1.43 (m, 2H).
LC/MS: (ES) *m/z* 465 (M + H)+

Example 8 6-({4-Hydroxy-4-[2-(2-methoxy-quinolin-8-yl)-ethyl]-cyclohexylamino}-methyl)-4H-pyrido[3,2-b][1,4]thiazin-3-one



The title compound was prepared in 57% purified yield according to the method described for (7k) above, substituting the carboxaldehyde with 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-b][1,4]thiazine-6-carboxaldehyde (1j) affording a light yellow foam.

^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, 1H); 7.55 (d, 1H); 7.48 (d, 1H); 7.29 (t, 1H); 7.18 (d, 1H); 6.93 (d, 1H); 6.88 (d, 1H); 4.61 (s, 2H); 4.06 (s, 3H); 3.86 (s, 2H); 3.25 (m, 2H); 2.52 (m, 1H); 1.89 (m, 2H); 1.79 (m, 2H); 1.76 (m, 2H); 1.59 (m, 2H); 1.43 (m, 2H).
LC/MS: (ES) *m/z* 479 (M + H)+

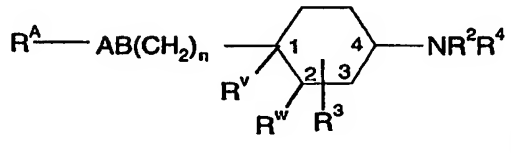
Biological Activity

The MIC (μg/ml) of test compounds against various organisms was determined including: **S. epidermidis CL7, S. aureus WCUH29, S. pneumoniae 1629, S. pyogenes CN10, H. influenzae ATCC 49247, E.faecalis 2, M. catarrhalis Ravasio, E. coli 7623.**

Examples 5, 7 and 8 have an MIC≤2μg/ml versus all these organisms
Examples 1 and 3 have an MIC≤8μg/ml versus all these organisms
Example 6 has an MIC≤2μg/ml versus all these organisms
Example 4 has an MIC ≤16μg/ml versus at least one of these organisms

Claims

1. A compound of formula (I) or a pharmaceutically acceptable derivative thereof:

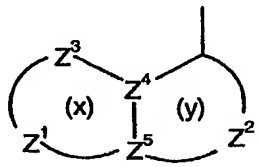


(I)

wherein:

R^V and R^W are hydrogen or R^V and R^W together are a bond;

R^A is an optionally substituted bicyclic carbocyclic or heterocyclic ring system of structure:



containing 0-3 heteroatoms in each ring in which:

at least one of rings (x) and (y) is aromatic;

one of Z^4 and Z^5 is C or N and the other is C;

Z^3 is N, NR^{13}, O, $S(O)_X$, CO, CR^1 or CR^1R^{1a};

Z^1 and Z^2 are independantly a 2 or 3 atom linker group each atom of which is independently selected from N, NR^{13}, O, $S(O)_X$, CO, CR^1 and CR^1R^{1a};
such that each ring is independently substituted with 0-3 groups R^1 and/or R^{1a};

R^1 and R^{1a} are independently selected from hydrogen; hydroxy; (C_{1-6}) alkoxy optionally substituted by (C_{1-6})alkoxy, amino, piperidyl, guanidino or amidino any of which is optionally N-substituted by one or two (C_{1-6})alkyl, acyl or (C_{1-6})alkylsulphonyl groups, CONH2, hydroxy, (C_{1-6})alkylthio, heterocyclylthio, heterocyclyloxy, arylthio, aryloxy, acylthio, acyloxy or (C_{1-6})alkylsulphonyloxy; (C_{1-6})alkoxy-substituted (C_{1-6})alkyl; hydroxy (C_{1-6})alkyl; halogen; (C_{1-6})alkyl; (C_{1-6})alkylthio; trifluromethyl; trifluoromethoxy; cyano; carboxy; nitro; azido; acyl; acyloxy; acylthio; (C_{1-6})alkylsulphonyl; (C_{1-6})alkylsulphoxide; arylsulphonyl; arylsulphoxide or an amino, piperidyl, guanidino or amidino group optionally N-substituted by one or two (C_{1-6})alkyl, acyl or (C_{1-6})alkylsulphonyl groups, or when Z^3 and the adjacent atom are CR^1 and CR^{1a}, R^1 and R^{1a} may together represent (C_{1-2})alkylenedioxy, provided that R^1 and R^{1a}, on the same carbon atom are not both optionally substituted hydroxy or amino;

provided that

(i) when R^A is optionally substituted quinolin-4-yl:

it is unsubstituted in the 6-position; or

it is substituted by at least one hydroxy (C_{1-6})alkyl, cyano or carboxy group at the 2-, 5-, 6-, 7- or 8-position; or

it is substituted by at least one trifluoromethoxy group; or

R^3 is halogen;

(ii) when R^A is optionally substituted quinazolin-4-yl, cinnolin-4-yl, 1,5-naphthyridin-4-yl, 1,7-naphthyridin-4-yl or 1,8-naphthyridin-4-yl:

it is substituted by at least one hydroxy (C_{1-6})alkyl, cyano or carboxy group at the 2-, 5-, 6-, 7- or 8-position as available; or

it is substituted by at least one trifluoromethoxy group; or

R^3 is halogen;

R^2 is hydrogen, or (C_{1-4})alkyl or (C_{2-4})alkenyl optionally substituted with 1 to 3 groups selected from:
amino optionally substituted by one or two (C_{1-4})alkyl groups; carboxy; (C_{1-4})alkoxycarbonyl; (C_{1-4})alkylcarbonyl; (C_{2-4})alkenyloxycarbonyl; (C_{2-4})alkenylcarbonyl; aminocarbonyl wherein the amino group is optionally substituted by hydroxy, (C_{1-4})alkyl, hydroxy(C_{1-4})alkyl, aminocarbonyl(C_{1-4})alkyl, (C_{2-4})alkenyl, (C_{1-4})alkylsulphonyl, trifluoromethylsulphonyl, (C_{2-4})alkenylsulphonyl, (C_{1-4})alkoxycarbonyl, (C_{1-4})alkylcarbonyl, (C_{2-4})alkenyloxycarbonyl or (C_{2-4})alkenylcarbonyl; cyano; tetrazolyl; 2-oxo-oxazolidinyl optionally substituted by R^{10}; 3-hydroxy-3-cyclobutene-1,2-dione-4-yl; 2,4-thiazolidinedione-5-yl; tetrazol-5-ylaminocarbonyl; 1,2,4-triazol-5-yl optionally substituted by R^{10}; 5-oxo-1,2,4-oxadiazol-3-yl; halogen; (C_{1-4})alkylthio; trifluoromethyl; hydroxy optionally substituted by (C_{1-4})alkyl, (C_{2-4})alkenyl, (C_{1-4})alkoxycarbonyl, (C_{1-4})alkylcarbonyl, (C_{2-4})alkenyloxycarbonyl, (C_{2-4})alkenylcarbonyl; oxo; (C_{1-4})alkylsulphonyl; (C_{2-4})alkenylsulphonyl; or (C_{1-4})aminosulphonyl wherein the amino group is optionally substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl;

R^3 is hydrogen; or
when R^V and R^W are a bond, R^3 is in the 2-, 3- or 4- position and when R^V and R^W are not a bond, R^3 is in the 1-, 2-, 3- or 4-position and R^3 is:
carboxy; (C_{1-6})alkoxycarbonyl; aminocarbonyl wherein the amino group is optionally substituted by hydroxy, (C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, aminocarbonyl(C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylsulphonyl, trifluoromethylsulphonyl, (C_{2-6})alkenylsulphonyl, $(C_{1-}$

(C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl or (C_{2-6})alkenylcarbonyl and optionally further substituted by (C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, aminocarbonyl(C_{1-6})alkyl or (C_{2-6})alkenyl; cyano; tetrazolyl; 2-oxo-oxazolidinyl optionally substituted by R^{10}; 3-hydroxy-3-cyclobutene-1,2-dione-4-yl; 2,4-thiazolidinedione-5-yl; tetrazol-5-ylaminocarbonyl; 1,2,4-triazol-5-yl optionally substituted by R^{10}; or 5-oxo-1,2,4-oxadiazol-3-yl; or

(C_{1-4})alkyl or ethenyl optionally substituted with any of the groups listed above for R^3 and/or 0 to 2 groups R^{12} independently selected from:

halogen; (C_{1-6})alkylthio; trifluoromethyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; (C_{2-6})alkenyloxycarbonyl; (C_{2-6})alkenylcarbonyl; hydroxy optionally substituted by (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylcarbonyl or (C_{2-6})alkenylcarbonyl; amino optionally mono- or disubstituted by (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylsulphonyl, (C_{2-6})alkenylsulphonyl or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl; aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, aminocarbonyl(C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl or (C_{2-6})alkenylcarbonyl and optionally further substituted by (C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, aminocarbonyl(C_{1-6})alkyl or (C_{2-6})alkenyl; oxo; (C_{1-6})alkylsulphonyl; (C_{2-6})alkenylsulphonyl; or (C_{1-6})aminosulphonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl; or

hydroxy optionally substituted by (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylcarbonyl or (C_{2-6})alkenylcarbonyl; or

amino optionally mono- or disubstituted by (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylsulphonyl, (C_{2-6})alkenylsulphonyl or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl; or

halogen;

provided that when R^3 is in the 4- position it is not optionally substituted hydroxyl or amino or halogen;

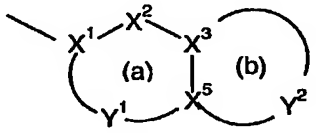
in addition when R^3 is disubstituted with a hydroxy or amino containing substituent and a carboxy containing substituent these may optionally together form a cyclic ester or amide linkage, respectively;

R^{10} is selected from (C_{1-4})alkyl and (C_{2-4})alkenyl either of which may be optionally substituted by a group R^{12} as defined above; carboxy; aminocarbonyl wherein the amino group is optionally substituted by hydroxy, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylsulphonyl, trifluoromethylsulphonyl, (C_{2-6})alkenylsulphonyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl or (C_{2-6})alkenylcarbonyl and optionally further substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl; (C_{1-6})alkylsulphonyl; trifluoromethylsulphonyl; (C_{2-6})alkenylsulphonyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; (C_{2-6})alkenyloxycarbonyl; and (C_{2-6})alkenylcarbonyl;

R^4 is a group $-CH_2-R^5{}_1$ in which $R^5{}_1$ is selected from:

(C_{4-8})alkyl; hydroxy(C_{4-8})alkyl; (C_{1-4})alkoxy(C_{4-8})alkyl; (C_{1-4})alkanoyloxy(C_{4-8})alkyl; (C_{3-8})cycloalkyl(C_{4-8})alkyl; hydroxy-, (C_{1-6})alkoxy- or (C_{1-6})alkanoyloxy-(C_{3-8})cycloalkyl(C_{4-8})alkyl; cyano(C_{4-8})alkyl; (C_{4-8})alkenyl; (C_{4-8})alkynyl; tetrahydrofuryl; mono- or di-(C_{1-6})alkylamino(C_{4-8})alkyl; acylamino(C_{4-8})alkyl; (C_{1-6})alkyl- or acyl-aminocarbonyl(C_{4-8})alkyl; mono- or di- (C_{1-6})alkylamino(hydroxy) (C_{4-8})alkyl; or

R^4 is a group $-U-R^5{}_2$ where $R^5{}_2$ is an optionally substituted bicyclic carbocyclic or heterocyclic ring system (A):



(A)

containing up to four heteroatoms in each ring in which

at least one of rings (a) and (b) is aromatic;

X^1 is C or N when part of an aromatic ring or CR^{14} when part of a non aromatic ring;

X^2 is N, NR^{13}, O, $S(O)_X$, CO or CR^{14} when part of an aromatic or non-aromatic ring or may in addition be $CR^{14}R^{15}$ when part of a non aromatic ring;

X^3 and X^5 are independently N or C;

Y^1 is a 0 to 4 atom linker group each atom of which is independently selected from N, NR^{13}, O, $S(O)_x$, CO and CR^{14} when part of an aromatic or non-aromatic ring or may additionally be $CR^{14}R^{15}$ when part of a non aromatic ring,

Y^2 is a 2 to 6 atom linker group, each atom of Y^2 being independently selected from N, NR^{13}, O, $S(O)_x$, CO and CR^{14} when part of an aromatic or non-aromatic ring or may additionally be $CR^{14}R^{15}$ when part of a non aromatic ring;

each of R^{14} and R^{15} is independently selected from: H; (C_{1-4})alkylthio; halo; carboxy(C_{1-4})alkyl; halo(C_{1-4})alkoxy; halo(C_{1-4})alkyl; (C_{1-4})alkyl; (C_{2-4})alkenyl; (C_{1-4})alkoxycarbonyl; formyl; (C_{1-4})alkylcarbonyl; (C_{2-4})alkenyloxycarbonyl; (C_{2-4})alkenylcarbonyl; (C_{1-4})alkylcarbonyloxy; (C_{1-4})alkoxycarbonyl(C_{1-4})alkyl; hydroxy; hydroxy(C_{1-4})alkyl; mercapto(C_{1-4})alkyl; (C_{1-4})alkoxy; nitro; cyano; carboxy; amino or aminocarbonyl optionally substituted as for corresponding substituents in R^3; (C_{1-4})alkylsulphonyl; (C_{2-4})alkenylsulphonyl; or aminosulphonyl wherein the amino group is optionally substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl; aryl; aryl(C_{1-4})alkyl; aryl(C_{1-4})alkoxy;

each R^{13} is independently H; trifluoromethyl; (C_{1-4})alkyl optionally substituted by hydroxy, carboxy, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkoxy, (C_{1-6})alkylthio, halo or trifluoromethyl; (C_{2-4})alkenyl; aryl; aryl (C_{1-4})alkyl; arylcarbonyl; heteroarylcarbonyl; (C_{1-4})alkoxycarbonyl; (C_{1-4})alkylcarbonyl; formyl; (C_{1-6})alkylsulphonyl; or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-4})alkoxycarbonyl, (C_{1-4})alkylcarbonyl, (C_{2-4})alkenyloxycarbonyl, (C_{2-4})alkenylcarbonyl, (C_{1-4})alkyl or (C_{2-4})alkenyl and optionally further substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl;

each x is independently 0, 1 or 2;

U is CO, SO_2 or CH_2; or

R^4 is a group $-X^{1a}-X^{2a}-X^{3a}-X^{4a}$ in which:

X^{1a} is CH_2, CO or SO_2;

X^{2a} is $CR^{14a}R^{15a}$;

X^{3a} is NR^{13a}, O, S, SO_2 or $CR^{14a}R^{15a}$; wherein:

each of R^{14a} and R^{15a} is independently selected from the groups listed above for R^{14} and R^{15}, provided that R^{14a} and R^{15a} on the same carbon atom are not both selected from optionally substituted hydroxy and optionally substituted amino; or

R^{14a} and R^{15a} together represent oxo;

R^{13a} is hydrogen; trifluoromethyl; (C_{1-6})alkyl; (C_{2-6})alkenyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, $(C_{2-}$

6)alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl, (C_{1-6})alkyl or (C_{2-6})alkenyl and optionally further substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl; or

two R^{14a} groups or an R^{13a} and an R^{14a} group on adjacent atoms together represent a bond and the remaining R^{13a}, R^{14a} and R^{15a} groups are as above defined; or

two R^{14a} groups and two R^{15a} groups on adjacent atoms together represent bonds such that X^{2a} and X^{3a} is triple bonded;

X^{4a} is phenyl or C or N linked monocyclic aromatic 5- or 6-membered heterocycle containing up to four heteroatoms selected from O, S and N and: optionally C-substituted by up to three groups selected from (C_{1-4})alkylthio; halo; carboxy(C_{1-4})alkyl; halo(C_{1-4})alkoxy; halo(C_{1-4})alkyl; (C_{1-4})alkyl; (C_{2-4})alkenyl; (C_{1-4})alkoxycarbonyl; formyl; (C_{1-4})alkylcarbonyl; (C_{2-4})alkenyloxycarbonyl; (C_{2-4})alkenylcarbonyl; (C_{1-4})alkylcarbonyloxy; (C_{1-4})alkoxycarbonyl(C_{1-4})alkyl; hydroxy; hydroxy(C_{1-4})alkyl; mercapto(C_{1-4})alkyl; (C_{1-4})alkoxy; nitro; cyano; carboxy; amino or aminocarbonyl optionally substituted as for corresponding substituents in R^3; (C_{1-4})alkylsulphonyl; (C_{2-4})alkenylsulphonyl; or aminosulphonyl wherein the amino group is optionally substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl; aryl, aryl(C_{1-4})alkyl or aryl(C_{1-4})alkoxy; and

optionally N substituted by trifluoromethyl; (C_{1-4})alkyl optionally substituted by hydroxy, (C_{1-6})alkoxy, (C_{1-6})alkylthio, halo or trifluoromethyl; (C_{2-4})alkenyl; aryl; aryl(C_{1-4})alkyl; (C_{1-4})alkoxycarbonyl; (C_{1-4})alkylcarbonyl; formyl; (C_{1-6})alkylsulphonyl; or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-4})alkoxycarbonyl, (C_{1-4})alkylcarbonyl, (C_{2-4})alkenyloxycarbonyl, (C_{2-4})alkenylcarbonyl, (C_{1-4})alkyl or (C_{2-4})alkenyl and optionally further substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl;

n is 0 or 1 and AB is $NR^{11}CO$, $CONR^{11}$, $CO\text{-}CR^8R^9$, $CR^6R^7\text{-}CO$, $O\text{-}CR^8R^9$, $CR^6R^7\text{-}O$, $NHR^{11}\text{-}CR^8R^9$, $CR^6R^7\text{-}NHR^{11}$, $NR^{11}SO_2$, $CR^6R^7\text{-}SO_2$ or $CR^6R^7\text{-}CR^8R^9$, provided that when R^V and R^W are a bond and n=0, B is not NR^{11}, O or SO_2, or n is 0 and AB is NH-CO-NH or NH-CO-O and R^V/R^W are not a bond; or n is 0 and AB is $CR^6R^7SO_2NR^2$, $CR^6R^7CONR^2$ or $CR^6R^7CH_2NR^2$ and R^V/R^W are not a bond;

provided that R^6 and R^7, and R^8 and R^9 are not both optionally substituted hydroxy or amino;

and wherein:

each of R^6, R^7, R^8 and R^9 is independently selected from: H; (C_{1-6})alkoxy; (C_{1-6})alkylthio; halo; trifluoromethyl; azido; (C_{1-6})alkyl; (C_{2-6})alkenyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; (C_{2-6})alkenyloxycarbonyl; (C_{2-6})alkenylcarbonyl; hydroxy, amino or aminocarbonyl optionally substituted as for

corresponding substituents in R^3; (C_{1-6})alkylsulphonyl; (C_{2-6})alkenylsulphonyl; or (C_{1-6})aminosulphonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl;
or R^6 and R^8 together represent a bond and R^7 and R^9 are as above defined;

and each R^{11} is independently H; trifluoromethyl; (C_{1-6})alkyl; (C_{2-6})alkenyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl, (C_{1-6})alkyl or (C_{2-6})alkenyl and optionally further substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl;

or where one of R^3 and R^6, R^7, R^8 or R^9 contains a carboxy group and the other contains a hydroxy or amino group they may together form a cyclic ester or amide linkage or where R^3 contains a carboxy group and A or B is NH they may be condensed to form a cyclic amide.

The invention also provides the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof in the manufacture of a medicament for use in the treatment of bacterial infections in mammals.

The invention also provides a pharmaceutical composition, in particular for use in the treatment of bacterial infections in mammals, comprising a compound of formula (I), or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable carrier.

The invention further provides a method of treatment of bacterial infections in mammals, particularly in man, which method comprises the administration to a mammal in need of such treatment of an effective amount of a a compound of formula (I), or a pharmaceutically acceptable derivative thereof.

2. A compound according to claim 1 wherein R^A is optionally substituted isoquinolin-5-yl, quinolin-8-yl, thieno[3,2-b]pyridin-7-yl or 2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-8-yl.

3. A compound according to any preceding claim wherein R^1 is methoxy or halogen and R^{1a} is H.

4. A compound according to any preceding claim wherein R^2 is hydrogen.

5. A compound according to any preceding claim wherein R^3 is hydrogen or hydroxy substituted in the 1-or 3-position.

6. A compound according to any preceding claim wherein n is 0 and either A and B are both CH_2, A is CHOH or CH_2 and B is CH_2 or A is NH and B is CO, and $AB(CH_2)_n$ and NR^2R^4 are trans.

7. A compound according to any preceding claim wherein R^4 is $-U-R^5{}_2$, the group –U– is $-CH_2-$, and $R^5{}_2$ is an aromatic heterocyclic ring (A) having 8-11 ring atoms including 2-4 heteroatoms of which at least one is N or NR^{13} in which Y^2 contains 2-3 heteroatoms, one of which is S and 1-2 are N, with one N bonded to X^3, or the heterocyclic ring (A) has ring (a) aromatic selected from optionally substituted benzo and pyrido and ring (b) non-aromatic and Y^2 has 3-5 atoms including a heteroatom bonded to X^5 selected from O, S or NR^{13}, where R^{13} is other than hydrogen, and NHCO bonded via N to X^3, or O bonded to X^3.

8. A compound according to any of claims 1 to 6 wherein $R^5{}_2$ is selected from:3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl
3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-yl
7-chloro-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-yl
7-fluoro-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-yl.

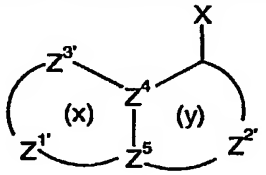
9. A compound selected from:
1-Hydroxy-*t*-4-[(3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazin-6-ylmethyl)-amino]-*r*-cyclohexanecarboxylic acid thieno[3,2-b]pyridin-7-ylamide
1-Hydroxy-*t*-4-[(3-oxo-3,4-dihydro-2H -pyrido[3,2-b][1,4]thiazin-6-ylmethyl)-amino]-*r*-cyclohexanecarboxylic acid (2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-8-yl)-amide
trans-4-[(3-Oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazin-6-ylmethyl)-amino]-cyclohexanecarboxylic acid quinolin-4-ylamide
trans-4-[(3-Oxo-3,4-dihydro-2H-benzo[1,4]thiazin-6-ylmethyl)-amino]-cyclohexanecarboxylic acid isoquinolin-5-ylamide
1-Hydroxy-*t*-4-[(3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazin-6-ylmethyl)-amino]-*r*-cyclohexanecarboxylic acid (2-methoxy-quinolin-8-yl)-amide
4-[(3,4-Dihydro-2H-pyrido[3,2-b][1,4]thiazin-6-ylmethyl)-amino]-1-hydroxy-cyclohexanecarboxylic acid (2-methoxy-quinolin-8-yl)-amide
6-({4-Hydroxy-4-[2-(2-methoxy-quinolin-8-yl)-ethyl]-cyclohexylamino}-methyl)-4H-pyrido[3,2-b][1,4]oxazin-3-one
6-({4-Hydroxy-4-[2-(2-methoxy-quinolin-8-yl)-ethyl]-cyclohexylamino}-methyl)-4H-pyrido[3,2-b][1,4]thiazin-3-one
or a pharmaceutically acceptable derivative thereof.

10. A method of treatment of bacterial infections in mammals, particularly in man, which method comprises the administration to a mammal in need of such treatment an effective amount of a compound according to claim 1.

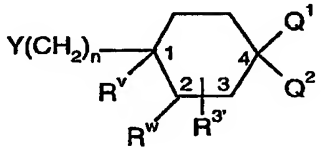
11. The use of a compound according to claim 1, in the manufacture of a medicament for use in the treatment of bacterial infections in mammals.

12. A pharmaceutical composition comprising a compound according to claim 1, and a pharmaceutically acceptable carrier.

13. A process for preparing a compound according to claim 1, which process comprises reacting a compound of formula (IV) with a compound of formula (V):



(IV)



(V)

wherein n is as defined in formula (I); $Z^{1'}$, $Z^{2'}$, $Z^{3'}R^{1'}$ and $R^{3'}$ are Z^1, Z^2, Z^3, R^1 and R^3 as defined in formula (I) or groups convertible thereto; Z^4, Z^5, R^v and R^w are as defined in formula (I);

Q^1 is $NR^{2'}R^{4'}$ or a group convertible thereto wherein $R^{2'}$ and $R^{4'}$ are R^2 and R^4 as defined in formula (I) or groups convertible thereto and Q^2 is H or $R^{3'}$ or Q^1 and Q^2 together form an optionally protected oxo group;

and X and Y may be the following combinations:

(i) one of X and Y is CO_2R^y and the other is $CH_2CO_2R^x$;

(ii) X is CHR^6R^7 and Y is $C(=O)R^9$;

(iii) X is $CR^7=PR^z{}_3$ and Y is $C(=O)R^9$;

(iv) X is $C(=O)R^7$ and Y is $CR^9=PR^z{}_3$;

(v) one of Y and X is COW and the other is $NHR^{11'}$, NCO or $NR11'COW$;

(vi) X is $NHR^{11'}$ and Y is $C(=O)R^8$ or X is $C(=O)R^6$ and Y is $NHR^{11'}$;

(vii) X is $NHR^{11'}$ and Y is CR^8R^9W;

(viii) X is W or OH and Y is CH_2OH;

(ix) X is $NHR^{11'}$ and Y is SO_2W;

(x) one of X and Y is $(CH_2)_p$-W and the other is $(CH_2)_qNHR^{11'}$, $(CH_2)_qOH$, $(CH_2)_qSH$ or $(CH_2)_qSCOR^x$ where p+q=1;

(xi) one of X and Y is OH and the other is $-CH=N_2$;

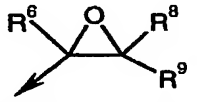
(xii) X is NCO and Y is OH or NH_2;

(xiii) X is $CR^6R^7SO_2W$, A'COW, $CR^6{=}CH_2$ or oxirane and Y is $NHR^{2'}$;

(xiv) Xis W and Y is $CONHR^{11}$ or $OCONH_2$

(xv) X is W and Y is -C≡CH followed by hydrogenation of the intermediate –C≡C- group;

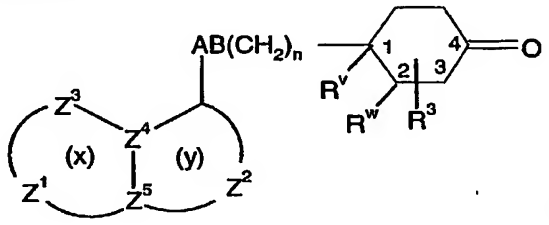
in which W is a leaving group, e.g. halo, methanesulphonyloxy, trifluoromethanesulphonyloxy or imidazolyl; R^X and R^Y are (C_{1-6})alkyl; R^Z is aryl or (C_{1-6})alkyl; A' and $NR^{11'}$ are A and NR^{11} as defined in formula (I), or groups convertible thereto; and oxirane is:



wherein R^6, R^8 and R^9 are as defined in formula (I);

and thereafter optionally or as necessary converting Q^1 and Q^2 to $NR^{2'}R^{4'}$; converting A', $Z^{1'}$, $Z^{2'}$, $Z^{3'}$, $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$ and $NR^{11'}$ to A, Z^1, Z^2, Z^3, R^1, R^2, R^3, R^4 and $NR^{11'}$; converting A-B to other A-B, interconverting R^V, R^W, R^1, R^2, R^3 and/or R^4, and/or forming a pharmaceutically acceptable derivative thereof.

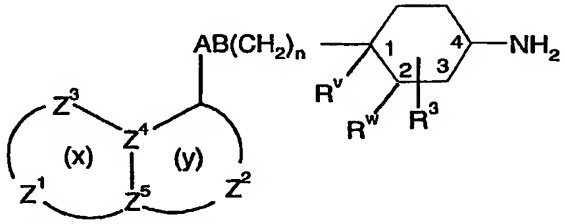
14. A compound of formula (VI):



(VI)

wherein the variables are as described for formula (I).

15. A compound of formula (VII):



wherein the variables are as described for formula (I).

Abstract

Medicaments

Cyclohexane and cyclohexene derivatives and pharmaceutically acceptable derivatives thereof useful in methods of treatment of bacterial infections in mammals, particularly man.